```
     FILE 'USPATFULL' ENTERED AT 18:56:23 ON 28 OCT 2003
L1          3416 S FATIGUE/AB
L2          2393 S FATIGUE/CLM
L3          1057 S L1 AND L2
L4           117 S L3 AND (TREAT?/AB AND TREAT?/CLM)
L5            12 S L4 AND RADIATION
L6           984 S L3  NOT (CHRONIC FATIGUE)
L7            70 S L6 AND (TREAT?/AB AND TREAT?/CLM)
L8           715 S TIREDNESS
L9             4 S RADIATION (1S) TREAT? (3S) L8
L10            3 S COX-2 AND L8
L11        60373 S TIREDNESS OR FATIGUE
L12            7 S L11 (2S) TREAT? (2S) NSAID
L13          984 S L6
L14          306 S L11 (1S) (PROSTAGLADIN? OR AUTOIMMUNE? OR CYCLOXYGENASE OR CY
L15           59 S L11 (1S) (PROSTAGLADIN? OR AUTOIMMUNE? OR CYCLOXYGENASE OR CY
L16       287715 S RADIOTHERAPY OR RADIOTREATMENT OR RADIATION
L17        49111 S (SIDE OR ADVERSE) (2S) L16
L18          113 S L11 (1S) L17
L19           96 S L18 NOT (CHRONIC FATIGUE)
L20         3432 S L11 (15A) (CAUSED? OR RESULTED?)
L21         2938 S L11 (10A) (CAUSED? OR RESULTED?)

     FILE 'CAPLUS' ENTERED AT 19:48:30 ON 28 OCT 2003
L22         1968 S L11 (10A) (CAUSED? OR RESULTED?)
L23         1884 S L11/AB (10A) (CAUSED? OR RESULTED?)/AB
L24           30 S L23 AND (ANTIBIOTIC? OR RADIATION?)

=> save cox2fatigue/l
ENTER L#, L# RANGE, ALL, OR (END):all
L# LIST L1-L24 HAS BEEN SAVED AS 'COX2FATIGUE/L'
  75% OF LIMIT FOR SAVED L# LISTS REACHED
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L24 ANSWER 37 OF 37 USPATFULL on STN

SUMM Patients who have significant inflammatory processes often have signs and symptoms of inflammation that are well known, such as fever, **fatigue**, loss of appetite, low blood pressure, and sometimes abnormalities in the amount of circulating white blood cells including both elevation and depression of their numbers, but these signs and symptoms are neither sensitive nor specific to the presence of inflammation. Many diseases and physical conditions, such as those listed above will cause **inflammatory responses** which can be noted in the blood. These **inflammatory responses** can frequently occur before more specific signs and symptoms of disease can be identified, and thus the detection of the presence of inflammation may allow more prompt diagnosis and treatment of the underlying condition. The best known and most widely used blood test indicator of inflammation is the erythrocyte sedimentation rate or ESR. The ESR was discovered by Fahraeus and popularized and improved by Wintrobe and Westergren. The Westergren erythrocyte sedimentation rate, or Westergren ESR, or WESR, which is sensitive to global elevations in inflammatory proteins is performed by measuring the distance the erythrocytes have sedimented in 60 minutes in a sample of anticoagulated blood which has been placed in a 200 mm long tube of defined dimensions. It has been an enduring laboratory test for both screening patients on an initial visit to a physician, and for following the evolution of the inflammatory condition in return visits. Despite the widespread use of the ESR procedure, there are certain drawbacks to this test which relate to, among other things, the amount of blood used to perform the test (at least one milliliter, which is a large amount for an infant); the amount of time needed to perform the test (one hour), and the fact that the test should optimally be performed within two hours of obtaining the blood. The ESR performed in the manner described by Wintrobe and Westergren is also affected by factors that may not indicate the presence or absence of inflammation such as: the presence of abnormally shaped red cells; the presence of proteins affecting the viscosity of the blood; the presence of antibody or cold agglutinens directed against red blood cells; the general level of gamma globulins even if they are not directed against the red cells; and deviations from verticality of the ESR tube while the test is being performed, as well as ambient temperature and vibration. Physicians therefore have attempted to develop other tests for inflammation that may be easier or quicker, or more sensitive or specific. Such tests include the C reactive protein or CRP; the white blood cell count; the granulocyte count (a component of the white blood cell count); the orosomucoid protein; the hematocrit or hemoglobin; and the fibrinogen. A total of at least sixteen tests have been used to monitor inflammation. All of these tests have advantages, as well as disadvantages, but none of them have been shown to be superior to the ESR.

ACCESSION NUMBER:	96:29474 USPATFULL
TITLE:	Determination of an individual's inflammation index from whole blood fibrinogen and hematocrit or hemoglobin measurements
INVENTOR(S):	Bull, Brian S., 24489 Barton Rd., Loma Linda, CA, United States 92354 Levine, Robert A., 31 Pilgrim La., Guilford, CT, United States 06437 Wardlaw, Stephen C., 191 N. Cove Rd., Old Saybrook, CT, United States 06475

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5506145		19960409	
APPLICATION INFO.:	US 1994-348345		19941202	(8)
DOCUMENT TYPE:	Utility			

FILE SEGMENT: Granted
PRIMARY EXAMINER: Warden, Jill
ASSISTANT EXAMINER: Wallenhorst, Maureen M.
LEGAL REPRESENTATIVE: Jones, William W.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 353
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=>

L3 ANSWER 43 OF 51 USPATFULL on STN

DETD The present invention also relates to methods for the treatment of certain diseases and medical conditions (many of which can be characterized as **inflammatory** diseases) that are mediated by TNF, as well as the related sequela and symptoms associated therewith. A non-exclusive list of acute and chronic TNF-mediated diseases includes but is not limited to the following: cachexia/anorexia; cancer (e.g., leukemias); chronic **fatigue** syndrome; depression; diabetes (e.g., juvenile onset Type 1 and diabetes mellitus); fibromyelgia or analgesia; graft versus host rejection; hyperalgesia; **inflammatory** bowel disease; ischemic, including cerebral ischemia (brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration); lung diseases (e.g., adult respiratory distress syndrome and pulmonary fibrosis); multiple sclerosis; neuroinflammatory diseases; ocular diseases; pain; pancreatitis; pulmonary fibrosis; reperfusion injury; rheumatic diseases (e.g., rheumatoid arthritis, osteoarthritis, juvenile (rheumatoid) arthritis, seronegative polyarthritis, ankylosing spondylitis, Reiter's syndrome and reactive arthritis, psoriatic arthritis, enteropathic arthritis, polymyositis, dermatomyositis, scleroderma, systemic sclerosis, vasculitis, cerebral vasculitis, Lyme disease, staphylococcal-induced ("septic") arthritis, Sjogren's syndrome, rheumatic fever, polychondritis and polymyalgia rheumatica and giant cell arteritis); septic shock; side effects from **radiation** therapy; systemic lupus erythematous; temporal mandibular joint disease; thyroiditis; tissue transplantation or an **inflammatory** condition resulting from strain, sprain, cartilage damage, trauma, orthopedic surgery, infection or other disease process.

DETD In a specific embodiment, the present invention is directed to the use of a TNFbp product(s) in combination (pretreatment, post-treatment or concurrent treatment) with any of one or more interleukin-1 inhibitors for the treatment of TNF-mediated diseases, including acute and chronic inflammation such as cachexia/anorexia; chronic **fatigue** syndrome, depression; diabetes (e.g., juvenile onset Type 1 and diabetes mellitus); fibromyelgia or analgesia; graft versus host rejection; hyperalgesia, **inflammatory** bowel disease; ischemic injury, including cerebral ischemia (e.g., brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration); lung diseases (e.g., ARDS and pulmonary fibrosis); multiple sclerosis, ocular diseases; pain; pancreatitis, reperfusion injury; rheumatic diseases (e.g., rheumatoid arthritis, osteoarthritis, juvenile (rheumatoid) arthritis, seronegative polyarthritis, ankylosing spondylitis, Reiter's syndrome and reactive arthritis, psoriatic arthritis, enteropathic arthritis, polymyositis, dermatomyositis, scleroderma, systemic sclerosis, vasculitis, cerebral vasculitis, Lyme disease, staphylococcal-induced ("septic") arthritis, Sjogren's syndrome, rheumatic fever, polychondritis and polymyalgia rheumatica and giant cell arteritis); septic shock; side effects from **radiation** therapy; temporal mandibular joint disease; tumor metastasis; or an **inflammatory** condition resulting from strain, sprain, cartilage damage, trauma, orthopedic surgery, infection or other disease processes. Classes of interleukin-1 inhibitors include interleukin-1 receptor antagonists (any compound capable of specifically preventing activation of cellular receptors to IL-1) such as IL-1ra, as described below; anti-IL-1 receptor monoclonal antibodies (e.g., EP 623674), the disclosure of which is hereby incorporated by reference; IL-1 binding proteins such as soluble IL-1 receptors (e.g., U.S. Pat. Nos. 5,492,888, 5,488,032, and 5,464,937, 5,319,071, and 5,180,812, the disclosures of which are hereby incorporated by reference); anti-IL-1 monoclonal antibodies (e.g., WO 9501997, WO 9402627, WO 9006371, U.S. Pat. No. 4,935,343, EP 364778, EP 267611 and EP 220063, the disclosures of which are hereby incorporated by reference); IL-1 receptor accessory proteins (e.g., WO 96/23067, the disclosure of which is hereby incorporated by

reference), and other compounds and proteins which block in vivo synthesis or extracellular release of IL-1.

PI US 6306820 B1 20011023

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L17 ANSWER 30 OF 32 USPATFULL on STN

DETD [0075] The disclosed TNF.alpha. inhibitors, compositions and combination therapies furthermore are useful for treating acute polyneuropathy; anorexia nervosa; Bell's palsy; **chronic fatigue syndrome**; transmissible dementia, including Creutzfeld-Jacob disease; demyelinating neuropathy; Guillain-Barre syndrome; vertebral disc disease; Gulf war syndrome; myasthenia gravis; silent cerebral ischemia; sleep disorders, including narcolepsy and sleep apnea; chronic neuronal degeneration; and stroke, including cerebral ischemic diseases.

DETD [0078] Various other medicaments used to treat the diseases described herein may also be administered concurrently with compositions comprising TNF.alpha. inhibitors, such as TNFR:Fc. Such medicaments include: NSAIDs; DMARDs; analgesics; topical steroids; systemic steroids (e.g., prednisone); cytokines; antagonists of inflammatory cytokines; antibodies against T cell surface proteins; oral retinoids; salicylic acid; and hydroxyurea. Suitable analgesics for such combinations include: acetaminophen, codeine, propoxyphene napsylate, oxycodone hydrochloride, hydrocodone bitartrate and tramadol. DMARDs suitable for such combinations include: azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine sulfate, methotrexate, leflunomide, minocycline, penicillamine, sulfasalazine, oral gold, gold sodium thiomalate and aurothioglucose. In addition, the TNFR:Fc or other TNFR mimic may be administered in combination with antimalarials or colchicine. NSAIDs suitable for the subject combination treatments include: salicylic acid (aspirin) and salicylate derivatives; ibuprofen; indomethacin; celecoxib (CELEBREX.RTM.); rofecoxib (VIOXX.RTM.); ketorolac; nambumetone; piroxicam; naproxen; oxaprozin; sulindac; ketoprofen; diclofenac; and other COX-1 and **COX-2** inhibitors, propionic acid derivatives, acetic acid derivatives, fumaric acid derivatives, carboxylic acid derivatives, butyric acid derivatives, oxicams, pyrazoles and pyrazolones, including newly developed anti-inflammatories.

ACCESSION NUMBER: 2001:155449 USPATFULL

TITLE: Soluble tumor necrosis factor receptor treatment of medical disorders

INVENTOR(S): Pluenneke, John D., Kansas City, MO, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001021380	A1	20010913
APPLICATION INFO.:	US 2001-778403	A1	20010207 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-726781, filed on 29 Nov 2000, PENDING Continuation-in-part of Ser. No. US 2000-602351, filed on 23 Jun 2000, PENDING Continuation-in-part of Ser. No. WO 2000-US10565, filed on 19 Apr 2000, UNKNOWN Continuation-in-part of Ser. No. US 1999-373828, filed on 13 Aug 1999, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-184864P	20000225 (60)
	US 1999-164676P	19991110 (60)
	US 1999-148234P	19990811 (60)
	US 1999-143959P	19990715 (60)
	US 1999-134320P	19990514 (60)
	US 1999-130074P	19990419 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: IMMUNEX CORPORATION, LAW DEPARTMENT, 51 UNIVERSITY STREET, SEATTLE, WA, 98101

NUMBER OF CLAIMS: 10

EXEMPLARY CLAIM: 1

LINE COUNT: 1238

L3 ANSWER 7 OF 7 USPATFULL on STN

DETD As this study was continued, 35 patients with CD were being **treated** with RMAT. 37% (13/35) of the patients developed a serum sickness-like illness during the first 4-6 weeks of **treatment**. The patients experienced flu-like symptoms such as fever, chills, moderate to severe arthralgia, back pain, anorexia, and **fatigue** . These symptoms generally lasted for a full week and dissipated over the following 3 weeks. With each patient, a majority of symptoms stopped within the first month of **treatment**. It was also found that these symptoms responded well to **Cox-2** inhibitors (celecoxib--200 mgm po qd) with no adverse effects or worsening of colitis noted during **treatment**. These observations suggest that the **Cox-2** inhibitors may help in controlling the initial side effects of RMAT. It is also thought that this serum sickness may be a Jarisch-Herxheimer reaction in response to the antimicrobial therapy.

ACCESSION NUMBER: 2001:167903 USPATFULL
TITLE: Crohn's disease diagnostic and treatment methods and compositions
INVENTOR(S): Shafran, Ira, 1316 Greencove Rd., Winter Park, FL, United States 32789

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6297015	B1	20011002	
APPLICATION INFO.:	US 1999-404095		19990923	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-101579P	19980924	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Le, Long V.
ASSISTANT EXAMINER: Cook, Lisa V
LEGAL REPRESENTATIVE: Allen, Dyer, Doppelt, Milbrath & Gilchrist, P.A.
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
LINE COUNT: 362
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L18 ANSWER 1 OF 1 CANCERLIT on STN
AN 1999700280 CANCERLIT
DN 99700280
TI Pre-Operative Twice Weekly Paclitaxel and **Radiation** Therapy in Locally Advanced Breast **Cancer** (LABC): Molecular Determinants of Pathological Response (Meeting abstract).
AU Formenti Silvia; Spicer Darc; Skinner Kristi; Cohen Deidr; Corso Francesc; Bettini Ann; Muggia Franc; Danenberg Kath; Danenberg Pete
CS Medicine, New York University, New York, New York.
SO Proc Annu Meet Am Soc Clin Oncol, (1999) 18 A282.
DT (MEETING ABSTRACTS)
LA English
FS Institute for Cell and Developmental Biology
EM 199910
ED Entered STN: 20000616
Last Updated on STN: 20000616
AB We designed a study of primary paclitaxel during **radiation** as a first-line treatment for locally advanced breast **cancer**. Pre-treatment tumor biopsies are obtained to study molecular determinant of pathological response. We used quantitative RT-PCR to analyze gene expressions of a) tubulin isoforms, which differentially modulate microtubule (MT) stability; b) stathmin, a regulator of MT dynamics; c) microtubule-associated protein 4 (MAP4), a p53-regulated protein that stabilizes MTs, and c) Cyclooxygenase-2 (**COX-2**), which regulates multiple genes involved in tumor progression. A total of 28 patients were accrued: 21 are evaluable for toxicity, clinical and pathological response. One patient developed grade IV esophagitis within the **radiation** field. Grade III toxicities were: moist/confluent skin desquamation at the breast/neck **radiated** sites in 3/21 patients, **fatigue** in 3/21 patients, arthralgia in 2/21 patients, myalgia in 1/21 patients and nausea in 1/21 patients. Four patients had post-surgical complications consisting of two delayed wound closures, and two wound infections. Clinical response was achieved in 19/21 (90%): 1CR, 18PR, 2SD. Seven patients achieved pathological response (33%): 5 complete responses (defined as: clearance of invasive **cancer** in the breast and axillary contents) and 2 pathological partial response (only residual microscopic foci of invasive breast **cancer**). Patients with pathological complete response (pCR) to the treatment had unchanged expression of stathmin, but had 4-fold lower expression of tubulin isoform III, 20-fold lower expression of tubulin IVb, 2-fold higher expression levels of MAP4 and a 30-fold lower expression of **COX-2**. The combination of twice a week paclitaxel and **radiation** constitutes a promising primary management for locally advanced breast **cancer**, with 90% clinical response and 33% pathological response rate at mastectomy. Preliminary results on MAP-4, tubulin isoform III and IVb and **COX-2** gene expression suggest that patients achieving pathological response can be identified prior to treatment based on quantitative gene expression profiles.

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NSWER 5 OF 53 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:635337 CAPLUS
DN 137:368031
TI Radiotherapy- and chemotherapy-induced normal tissue damage: the role of cytokines and adhesion molecules
AU Plevova, Pavlina
CS Department of Radiotherapy, University Hospital, Ostrava, Czech Rep.
SO Radiology and Oncology (2002), 36(2), 109-119
CODEN: RONCEM; ISSN: 1318-2099
PB Radiology and Oncology
DT Journal; General Review
LA English
CC 15-0 (Immunochemistry)
Section cross-reference(s): 1, 8, 14
AB A review. Background: Ionizing **radiation** and cytostatic agents used in cancer therapy exert damaging effects on normal tissues and induce a complex response at the cellular and mol. levels. Cytokines and adhesion mols. are involved in this response. Methods: Published data on the given topic have been reviewed. Results and conclusions: Various cytokines and adhesion mols., including tumor necrosis factor .alpha., interleukins-1,-2,-4, and -6, interferon .gamma., granulocyte macrophage- and macrophage- colony stimulating factors, transforming growth factor .beta., platelet-derived growth factor, insulin-like growth factor I, fibroblast and epidermal growth factors, platelet-activating factor, intercellular adhesion mol.-1, vascular cell adhesion mol.-1, E- and P-selectins are involved in the response of normal tissues to ionizing **radiation**- and chemotherapy-induced normal tissues damage. These mols. are also co-responsible for some side effects of these **treatment** modalities, including fever, anorexia and **fatigue**, suppression of hematopoiesis, both acute and late local tissue response.
ST review radiotherapy chemotherapy tissue damage cytokine adhesion mol
IT Animal tissue
Antitumor agents
Chemotherapy
Human
Neoplasm
Radiotherapy
(cytokines and adhesion mols. in radiotherapy and chemotherapy induced normal tissue damage)
IT Cell adhesion molecules
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(cytokines and adhesion mols. in radiotherapy and chemotherapy induced normal tissue damage)
IT **Radiation**
(damage; cytokines and adhesion mols. in radiotherapy and chemotherapy induced normal tissue damage)
RE.CNT 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L13 ANSWER 5 OF 6 CANCERLIT on STN
AN 87324967 CANCERLIT
DN 87324967 PubMed ID: 3631975
TI A case report of inflammatory breast cancer effectively treated with cis-platinum.
AU Nakagawa H; Kikuhara M; Sato M; Sakai K; Kimura S
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1987 Sep) 14 (9) 2767-70.
Journal code: 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS MEDLINE; Priority Journals
OS MEDLINE 87324967
EM 198710
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB A 50-year-old woman with bilateral **inflammatory** breast cancer (T4, N1b, M1, Stage IV) underwent right extended **radical** mastectomy and left modified **radical** mastectomy following pre-operative administration of carcinostatics (ADM, 5-FU) and irradiation. However, tumor recurrence was observed at the skin and right pleural cavity after the operation. Adriamycin-containing combination chemotherapy and **radiation** therapy were performed, but no significant response was obtained. CDDP was then administered intravenously at a daily dose of 62.5 mg/m2 at intervals of 60 days. The pleural effusion disappeared and the extent of skin metastasis was reduced, resulting in partial response which lasted for 90 days. The serum CEA level decreased from 13.1 ng/ml to 2.3 ng/ml. As the **side effects** of this therapy, slight nausea, vomiting and general **fatigue** were observed. This result suggested that CDDP is an effective drug for **inflammatory** breast cancer.
CT Check Tags: Case Report; Female; Human
*Breast Neoplasms: DT, drug therapy
Breast Neoplasms: SU, surgery

on STN DUPLICATE 4
AN 2002293285 EMBASE
TI The systemic inflammatory response, weight loss, performance status and survival in patients with inoperable non-small cell lung cancer.
AU Scott H.R.; McMillan D.C.; Forrest L.M.; Brown D.J.F.; McArdle C.S.; Milroy R.
CS Dr. D.C. McMillan, University Department of Surgery, Royal Infirmary, Glasgow G31 2ER, United Kingdom. d.c.mcmillan@clinmed.gla.ac.uk
SO British Journal of Cancer, (29 Jul 2002) 87/3 (264-267).
Refs: 21
ISSN: 0007-0920 CODEN: BJCAAI
CY United Kingdom
DT Journal; Article
FS 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
LA English
SL English
AB The relationship between the magnitude of systemic inflammatory response and the nutritional/functional parameters in patients with inoperable non-small cell lung cancer were studied. The extent of weight loss, albumin, C-reactive protein, performance status and quality of life was measured in 106 patients with inoperable non-small cell lung cancer (stages III and IV). Survival analysis was performed using the Cox proportional hazard model. The majority of patients were male and almost 80% had elevated circulating C-reactive protein concentrations (>10 mg 1(-1)). On multivariate analysis, age (P=0.012), tumour type (0.002), weight loss (P=0.056), C-reactive protein (P=0.047). Karnofsky performance status (P=0.002) and fatigue (P=0.046) were independent predictors of survival. The patients were grouped according to the magnitude of the C-reactive protein concentrations (.ltoreq.10, 11 - 100 and > 100 mg 1(-1)). An increase in the magnitude of the systemic **inflammatory response** was associated with increased weight loss (P=0.004), reduced albumin concentrations (P=0.001), reduced performance status (P=0.060), increased **fatigue** (P=0.011) and reduced survival (HR 1.936 95%Cl 1.414-2.650, P<0.001). These results indicate that the majority of patients with inoperable non-small cell lung cancer have evidence of a systemic **inflammatory response**. Furthermore, an increase in the magnitude of the systemic **inflammatory response** resulted in greater weight loss, poorer performance status, more **fatigue** and poorer survival.

CT Medical Descriptors:
*lung non small cell cancer
*systemic inflammatory response syndrome
weight reduction
performance
cancer survival
inoperable cancer
nutrition
functional assessment
quality of life
multivariate analysis
prognosis
fatigue
cancer staging
human
male
female
major clinical study
aged
adult
article
priority journal

Drug Descriptors:
albumin: EC, endogenous compound
C reactive protein: EC, endogenous compound
RN (C reactive protein) 9007-41-4

L24 ANSWER 32 OF 37 USPATFULL on STN

DETD [0192] An effective anti-microtubule therapy for inflammatory arthritis will accomplish one or more of the following: (i) decrease the severity of symptoms (pain, swelling and tenderness of affected joints; morning stiffness, weakness, **fatigue**. anorexia, weight loss); (ii) decrease the severity of clinical signs of the disease (thickening of the joint capsule, synovial hypertrophy, joint effusion, soft tissue contractures, decreased range of motion, ankylosis and fixed joint deformity); (iii) decrease the extra-articular manifestations of the disease (rheumatic nodules, vasculitis. ulmonary nodules, interstitial fibrosis, pericarditis, episclerit's, iritis, Felty's syndrome, osteoporosis); (iv) increase the frequency and duration of disease remission/symptom-free periods; (v) prevent fixed impairment and disability; and/or (vi) prevent/attenuate chronic progression of the disease. Pathologically, an effective anti-microtubule therapy for inflammatory arthritis will produce at least one of the following: (i) decrease the **inflammatory response**, (ii) disrupt the activity of inflammatory cytokines (such as IL-1, TNF.alpha., FGF, VEGF), (iii) inhibit synoviocyte proliferation, (iv) block matrix metalloproteinase activity, and/or (v). inhibit angiogenesis. An anti-microtubule agent will be administered systemically (orally, intravenously, or by intramuscular or subcutaneous injection) in the minimum dose to achieve the above mentioned results. For patients with only a small number of joints affected, or with disease more prominent in a limited number of joints, the anti-microtubule agent can be directly injected (intraarticular injection) into the affected joints.

ACCESSION NUMBER: 2002:22462 USPATFULL

TITLE: COMPOSITIONS AND METHODS FOR TREATING OR PREVENTING INFLAMMATORY DISEASES

INVENTOR(S): HUNTER, WILLIAM L., VANCOUVER, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002013298	A1	20020131
APPLICATION INFO.:	US 1999-368463	A1	19990804 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-88546, filed on 1 Jun 1998, PENDING Continuation-in-part of Ser. No. US 1997-980549, filed on 1 Dec 1997, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-32215P	19961202 (60)
	US 1997-63087P	19971024 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092

NUMBER OF CLAIMS: 45

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 110 Drawing Page(s)

LINE COUNT: 8318

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0812] As mentioned above, the formula 1 compounds, including those in the compound groups and embodiments disclosed herein, may be used to treat, prevent or slow the progression of one or more autoimmune allergic or inflammatory diseases, disorders, or conditions, or to ameliorate one or more symptoms thereof in a subject. These diseases and conditions include Addison's Disease, autoimmune hemolytic anemia, antiphospholipid syndrome, acute or chronic rheumatoid arthritis and other synovial disorders, an osteoarthritis including post-traumatic osteoarthritis and hypertrophic pulmonary osteoarthropathy, psoriatic arthritis, polyarthritis, epichondylitis, type I diabetes, type II diabetes, rheumatic carditis, bursitis, ankylosing spondylitis, multiple sclerosis, a dermatitis such as contact dermatitis, atopic dermatitis, exfoliative dermatitis or seborrheic dermatitis, mycosis fungoides, allergic encephalomyelitis, autoimmune glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Hashimoto's Thyroiditis, multiple sclerosis, myasthenia gravis, neuritis, bullous pemphigoid, pemphigus, polyendocrinopathies, purpura, Reiter's Disease, autoimmune thyroiditis, systemic lupus erythematosus, scleroderma, fibromyalgia, chronic **fatigue** syndrome, autoimmune pulmonary inflammation, Guillain-Barre Syndrome, type 1 or insulin dependent diabetes mellitus, autoimmune inflammatory eye disease, hepatitis C virus associated autoimmunity, postinfectious autoimmunity associated with, e.g., virus or bacterial infection such as a parvovirus such as human parvovirus B 19 or with rubella virus, autoimmune skin and muscle conditions such as pemphigus vulgaris, pemphigus foliaceus, systemic dermatomyositis or polymyositis or another inflammatory myopathy, myocarditis, asthma such as allergic asthma, allergic encephalomyelitis, allergic rhinitis, a vasculitis condition such as polyarteritis nodosa, giant cell arteritis or systemic necrotizing vasculitis, chronic and an acute or chronic inflammation condition such as chronic prostatitis, granulomatous prostatitis and malacoplakia, ischemia-reperfusion injury, endotoxin exposure, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, cachexia, sarcoidosis, inflammatory bowel disease, regional enteritis, ulcerative colitis, Crohn's disease, inflammatory bowel disease or inflammation associated with an infection, e.g., septic shock, sepsis, or systemic **inflammatory response** syndrome. Any of these diseases or conditions or their symptoms may be acute, chronic, mild, moderate, severe, stable or progressing before, during or after the time administration of the formula 1 compound to a subject such as a human, is initiated. In general, a detectable improvement is observed in the subject within a period of about 3 days to about 12 months after initiation of a dosing protocol, e.g., the severity of the disease or condition will detectably decrease, the rate of progression will detectably slow or the severity of a symptom(s) will detectably decrease.

SUMM [0816] In treating inflammation or any condition described herein where inflammation contributes to the condition, the formula 1 compounds may detectably modulate, e.g., decrease or increase, the expression or level or activity of one or more biomolecules associated with the prevention, establishment, maintenance or progression of the inflammation condition. Such biomolecules include one or more of carcinoembryonic antigen, prostate specific antigen, her2/neu, Bcl-XL, bcl-2, p53, IL-1.alpha., IL-1.beta., IL-6, or TNF.alpha., GATA-3, **COX-2**, NF.kappa.B, IkB, an IkB kinase, e.g., IkB kinase-.alpha., IkB kinase-.beta. or IkB kinase-.gamma., NFAT, a ras protein such as H-ras or K-ras, cyclin D, cyclin E xanthine oxidase, or their isoforms, homologs or mutant forms, which may have either reduced or enhanced biological activity(ies), and which may be detectably decreased. Biomolecules that can be detectably increased include IL-2, IFN.gamma., IL-12, T-bet, O6-methylguanine-DNA-methyltransferase, calcineurin, calmodulin, a superoxide dismutase (e.g., Mn, Zn or Cu), a tumor suppressor protein such as the retinoblastoma protein (Rb) or CDKN2A

(p16), BRCA1, BRCA2, MeCP2, MBD2, PTEN, NBR1, NBR2 or the isoforms, homologs or mutant forms, which may have either attenuated or enhanced biological activity(ies), of any of these molecules. One or more of these biomolecules may be modulated in any inflammation condition described herein.

SUMM [0842] In cases where a subject's blood cell deficiency is caused by, or associated with another therapy, the invention contemplates that the other therapy will continue, if this is reasonable under the circumstances. The timing of other therapies can precede, be simultaneous with, or follow the times of administration of the formula 1 compound(s) to the subject. For example, chemotherapy for some malignancies is accompanied by myelosuppression or a deficiency in one or more blood cell types, e.g., TP or NP. Continued treatment would be called for in some cases, and then the invention methods would be employed to deliver to the subject an effective amount of a formula 1 compound. Thus, alkylating agents, antimicrotubule agents, antimetabolites, topoisomerase 1 or 11 inhibitors, or platinum compounds such as one or more of mechlorethamine, vincristine, vinblastine, bleomycin, doxorubicin, epirubicin, tamoxifen, cyclophosphamide, etoposide, methotrexate, ifosfamide, melphalan, chlorambucil, busulfan, carmustine, lomustine, streptozocin, dacarbazine, vinorelbine, paclitaxel (taxol), docetaxel, cytosine arabinoside, hydroxyurea, fludarabine, 2'-chlorodeoxyadenosine, 2'-deoxycoformycin, 6-thioguanine, 6-mercaptopurine, 5-azacytidine, gemcitabine, arabinofuranosylguanine, daunorubicin, mitoxantrone, amsacrine, topotecan, irinotecan, cisplatin, carboplatin, pilcamycin, procarbazine, aspariginase, aminoglutethimide, actinomycin D, azathioprine and gallium nitrate may be administered in conjunction with administration of any formula 1 compound(s) that is disclosed herein. Treatments with other therapeutic agents such as heparin or nucleoside analogs such as 3-thiacytosine, azidothymidine or dideoxycytosine, or other antimicrobials such as cephalosporin, quinine, quinidine, gold salts (e.g., aurothioglucose), a fluoroquinolone (e.g., ciprofloxacin), clarithromycin, fluconazole, fusidic acid, gentamycin, nalidixic acid, penicillins, pentamidine, rifampicin, sulfa antibiotics, suramin or vancomycin may result in a blood cell deficiency(s) and they can thus be combined with administration of a formula 1 compound to treat the deficiency, or to ameliorate a symptom thereof. Similarly, anti-inflammatory drugs (e.g., salicylates, entanercept (a dimeric fusion coprising a portion of the human TNF receptor linked to the Fc protion of human IgG1 containing the C.sub.H2 and C.sub.H3 domain and hinge regions of IgG1) or a **COX-2** inhibitor such as celexicob (4-5[-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl] benzenesulfonamide) or rofecoxib (4-[4-methylsulfonyl)phenyl]-3-phenyl-2 (5H)-furanone) or an IL-1 receptor antagonist such as anakinra), cardiac drugs (e.g., digitoxin), .beta.-blockers or antihypertensive drugs (e.g., oxprenolol or captopril), diuretics (e.g., spironolactone), benzodiazepines, (e.g., diazepam) or antidepressants (e.g., amitriptyline, doxepin). Any of these methods also optionally include co-administration of one or more of the growth factors described above, e.g., IL-3, G-CSF, GM-CSF or TPO.

SUMM [0855] In many of the clinical conditions described herein, e.g., in cancers, infections, acute inflammation, chronic inflammation or autoimmunity, the formula 1 compounds can modulate, e.g., detectably decrease or increase, a biological activity(ies), protein or molecule level or RNA level of 1, 2, 3, 4, 5, 6 or more biomolecules that are involved in establishment, maintenance or progression of a disease, condition or symptom. Such biomolecules include 1, 2, 3, 4, 5, 6 or more of AP-1, a qyclooxygenase such as cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (**COX-2**), TNF.alpha., TNF.alpha. receptor 1, TNF.alpha. receptor 2, TNF receptor-associated factor, TNF.beta., TNF.beta. receptor, MIP-1.alpha., monocyte chemoattractant-1 (MCP-1), interferon gamma (IFN.gamma. or .gamma.IFN), IL-1.alpha.,

IL-1.beta., IL-1.alpha. receptor, IL-1.beta. receptor, IL-2, IL-3, IL-4, IL-4 receptor (IL-4R), IL-5, IL-6, IL-6 receptor (IL-6R), IL-8, IL-8 receptor (IL-8R), IL-10, IL-10 receptor (IL-10R), IL-12, an IL-12 receptor, (e.g., IL-12R.beta.2), IL-13, IL-15, IL-17, IL-18, nuclear factor kappa B (NF.kappa.B), AP-1, c-maf, v-maf, mafB, Nrl, mafK, mafG, the maf family protein p18, reactive oxygen species, e.g., hydrogen peroxide or superoxide ion (collectively ROS), a 17.beta.-hydroxysteroid dehydrogenase (17.beta.-HSD) or an 11.beta.-hydroxysteroid dehydrogenase (11.beta.-HSD), e.g., 11.beta.-HSD type 1,11.beta.-HSD type 2, 17.beta.-HSD type 1, 17.beta.-HSD type 2 or 17.beta.-HSD type 5, a steroid aromatase, e.g., cytochrome P450 aromatase, steroid 5.alpha.-reductase, serum or blood cortisol cytosolic phospholipase A2 (cPLA2), calcium-independent phospholipase A2 (iPLA2), a prostaglandin, e.g., prostaglandin E2 (PGE2) or prostaglandin D2 (PGD2), a leukotriene, e.g., leukotriene B4, inducible nitric oxide synthetase (iNOS), nitric oxide (NO), GM-CSF, RANTES (regulated on activation, normal T cells expressed and secreted), eotaxin, GATA-3, CCR1, CCR3, CCR4, CCR5, CXCR4,, in, e.g., a subject's cell(s) or tissue(s) or in enzyme, tissue or cell-based assays. In these subjects, the levels of other biomolecules, their RNAs or the level of their activity can be detectably modulated include IFN.alpha., INF.alpha. receptor, PPAR.alpha., PPAR.gamma., PPAR.delta. or a transcription factor such as T-bet is detectably increased. Other biomolecules or their polymorphs or homologs that the formula 1 compounds directly or indirectly modulate include one or more of, e.g., Janus kinase 1 (JAK1), Janus kinase 2 (JAK2), Janus kinase 3 (JAK3), signal transducer and activator of transcription 1 (STAT1), signal transducer and activator of transcription 2 (STAT2) and signal transducer and activator of transcription 3 (STAT3). The formula 1 compounds can modulate the other biologically active analogs of any these enzymes, chemokines, cytokines, their receptors or ligands, including their polymorphs or homologs. In some cells or tissues, one or more of these biomolecules may be detectably increased, while in other cells or tissues, the same biomolecule may be detectably decreased. Thus, the biomolecules that the formula 1 compounds can modulate, e.g., detectably increase or decrease, include the intracellular or extracellular level or biological activity of one or more enzyme, cytokine, cytokine receptor, chemokine and/or chemokine receptor.

SUMM [0858] Thus, in some embodiments, the level or a biological activity of 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more of **COX-2**, IL-1.beta., TNF.alpha., TNF.alpha. receptor 1, TNF.alpha. receptor 2, TNF receptor-associated factor, MIP-1.alpha., MCP-1, IFN.gamma., IL-4, IL-4R, IL-6, IL-6R, IL-8, IL-8R, IL-10, IL-10R, NF.kappa.B, IkB.alpha., AP-1, GATA-3, 11.beta.-HSD1, cPLA2, iPLA2, cortisol, ROS, PGE2, PGD2, leukotriene A4, leukotriene B4, leukotriene C4, iNOS or GM-CSF are optionally measured and they are generally detectably reduced, e.g., RNA or protein levels are reduced by about 10-95% or about 20-95% or more compared to suitable untreated controls. In these embodiments, the level or a biological activity of 4, 5, 6 or more of IFN.alpha., INF.alpha. receptor, IL-12, an IL-12 receptor, (e.g., IL-12R.beta.2), PPAR.alpha., PPAR.gamma.., and T-bet are optionally measured and they are generally detectably increased. In a chronic infection condition, e.g., HIV in humans, autoimmunity, a chronic fungal or parasite infection or in a precancer or cancer condition, e.g., benign prostatic hyperplasia, the progression of the condition may be slowed over a period of 1, 2, 3, 4, 5 or more years. In these embodiments, the subject's condition becomes more manageable with a reduced incidence or severity of side effects, e.g., a detectable halt, slowing, reversal or decreased incidence of wasting, dementia, CD4 cell count decreases or viral load increases, which tend to occur over time in HIV infected humans or a halt, slowing or reversal of pathogen or precancer or cancer cell replication. The detectable halt, slowing, reversal of the condition or decreased incidence of side effects can be

observed as a decrease of about 10% or more, e.g., about a 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or more decline.

DETD [1527] In patients examined at day 4, 43, 46 and 56 after 1 course of treatment, the level of RNA for several inflammation associated genes was analyzed. The RNA was obtained from circulating white blood cells from the patients and the uninfected volunteers. Peripheral blood was collected into a CPT-Vacutainer (Becton Dickinson) and PBMC isolation was performed according to the manufacturer's protocol. The PBMC were maintained in 1 mL of RPMI 1640 with 10% FCS ar 37.degree. C. for 3 hours and then lysed in lysis buffer (300 .mu.L MagnaPure.TM.). RNA levels from PBMC lysates were measured by preparation of cDNA using commercial AMV reverse transcriptase and PCR kits and protocols (First Strand cDNA Synthesis.TM., Roche Diagnostics; LightCycler FastStart DNA Sybr Green I.TM. Kit, Roche Diagnostics; LightCycler Primer sets, Search-LC, Heidelberg). The results generally showed a detectable decrease compared to baseline levels of about 40-98%, generally about 50-90% for RNA encoding IL-1.beta., TNF.alpha., IL-6, IL-8, IL-10, **COX-2** and MCP-1. The level of GM-CSF was increased at 43 days and decreased at all of the other time points. In the HIV-infected patients before treatment with BrEA, compared to healthy uninfected, i.e., not HIV infected, volunteers, there was a statistically significant (Mann-Whitney analysis) increase in RNA encoding IL-1 D, TNF.alpha., MIP-1 cc, IL-6, IL-8, **COX-2**, M-CSF, GM-CSF, MCP-1 and IFN.gamma.. BrEA treatment for 5 days thus resulted in a decrease in multiple inflammation-associated markers.

DETD [1536] After or during one treatment course of 100 mg of BrEA for 5 consecutive days, the HIV infected patients were examined at days 2-35. Day 1 was the first treatment day. The level of RNA for several inflammation associated genes was analyzed. At day 5, the results showed statistically significant decrease compared to baseline levels of RNA encoding IL-1.beta., TNF.alpha., GM-CSF, MIP-1.alpha. and **COX-2**, and a statistically significant increase in PPAR.gamma.. The RNA was obtained from circulating white blood cells from the patients and the uninfected volunteers essentially as described in the preceeding example. In the HIV-infected patients before treatment with BrEA, compared to healthy uninfected, i.e., not HIV infected, volunteers, there was a statistically significant (Mann-Whitney analysis) increase in RNA encoding IL-1.beta., TNF.alpha., MIP-1.alpha., IL-6, IL-8, IL-10, **COX-2**, M-CSF, RANTES, GM-CSF, MCP-1 and IFN.gamma.. At days 2-35 a statistically significant decrease ($p<0.001$ for all markers) in IL-1.beta., IL-6, TNF.alpha., GM-CSF, MIP-1.alpha., MCP-1 and **COX-2** transcripts was observed and an increase in PPAR.gamma. ($p=0.034$) was observed. Increases in PPAR.alpha. and t-Bet was also observed in the treated patients.

DETD [1545] A preliminary alysis of group 1 patients at day 5 indicated a general decrease in one or more inflammation-associated markers, e.g., IL-1.beta., TNF.alpha., MIP-1a, **COX-2** and GATA-3. In these HIV-infected patients before treatment with BrEA, compared to healthy uninfected, i.e., not HIV infected, volunteers, there were statistically significant (Mann-Whitney analysis, $p<0.001$) increases in RNA encoding IL-1.beta., TNF.alpha., MIP-1.beta., IL-6, IL-8, IL-10, **COX-2**, M-CSF, RANTES, GM-CSF, MCP-1 and IFN.gamma.. BrEA treatment in these patients was consistent with modulation of significant immune markers.

ACCESSION NUMBER: 2003:120747 USPATFULL
TITLE: Blood cell deficiency treatment method
INVENTOR(S): Ahlem, Clarence N., San Diego, CA, UNITED STATES
Reading, Christopher, San Diego, CA, UNITED STATES
Frincke, James, San Diego, CA, UNITED STATES
Stickney, Dwight, Granite Bay, CA, UNITED STATES
Lardy, Henry A., Madison, WI, UNITED STATES
Marwah, Padma, Middleton, WI, UNITED STATES

Marwah, Ashok, Middleton, WI, UNITED STATES
Prendergast, Patrick T., Straffan, IRELAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003083231	A1	20030501
APPLICATION INFO.:	US 2002-87929	A1	20020301 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-675470, filed on 28 Sep 2000, PENDING Continuation-in-part of Ser. No. US 2001-820483, filed on 29 Mar 2001, PENDING Continuation-in-part of Ser. No. US 2000-535675, filed on 23 Mar 2000, PENDING Continuation-in-part of Ser. No. US 1999-449004, filed on 24 Nov 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-449184, filed on 24 Nov 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-449042, filed on 24 Nov 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-461026, filed on 15 Dec 1999, ABANDONED Continuation-in-part of Ser. No. US 2000-586673, filed on 1 Jun 2000, ABANDONED Continuation-in-part of Ser. No. US 2000-586672, filed on 1 Jun 2000, ABANDONED Continuation-in-part of Ser. No. US 1999-414905, filed on 8 Oct 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-161453P	19991025 (60)
	US 2001-272624P	20010301 (60)
	US 2001-323016P	20010911 (60)
	US 2001-340045P	20011130 (60)
	US 2001-328738P	20011011 (60)
	US 2001-338015P	20011108 (60)
	US 2001-343523P	20011220 (60)
	US 1999-126056P	19991019 (60)
	US 1999-124087P	19990311 (60)
	US 1998-109923P	19981124 (60)
	US 1998-109924P	19981124 (60)
	US 1998-110127P	19981127 (60)
	US 1998-112206P	19981215 (60)
	US 1999-145823P	19990727 (60)
	US 1999-137745P	19990603 (60)
	US 1999-140028P	19990616 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HOLLIS-EDEN PHARMACEUTICALS, INC., 4435 EASTGATE MALL, SUITE 400, SAN DIEGO, CA, 92121
NUMBER OF CLAIMS: 45
EXEMPLARY CLAIM: 1
LINE COUNT: 19428
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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OF 51 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:449512 CAPLUS
DN 137:719
TI Inflammatory cytokine secretion inhibition with stressed blood cells
IN Bolton, Anthony Ernest; Mandel, Arkady; Sauder, Daniel Nathan
PA Vasogen Ireland Limited, Ire.
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K035-00
CC 1-7 (Pharmacology)
Section cross-reference(s): 15, 63
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002045723	A2	20020613	WO 2001-CA1745	20011205
	WO 2002045723	C2	20021219		
	WO 2002045723	A3	20030904		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	AU 2002015735	A5	20020618	AU 2002-15735	20011205
PRAI	CA 2000-2327631	A	20001205		
	WO 2001-CA1745	W	20011205		

AB A process of decreasing the expression of one or more of the **inflammatory** cytokines IFN-.gamma. and IL-6 from cells in a mammalian patient, comprises administering to the patient an effective amt. of stressed mammalian blood cells, said stressed cells having been extracorporeally subjected to at least one stressor selected from oxidative stress and UV **radiation**. These findings are indicative of the use of the process in the treatment for alleviation of chronic **fatigue** syndrome. Mice which received blood stressed with a gaseous oxygen/ozone mixt. and UV light at elevated temp. (42.5.degree.) had significantly reduced IFN-.gamma. and IL-6 as compared with sham treated animals and controls.

ST inflammatory cytokine secretion inhibition stressed blood cell; chronic fatigue syndrome treatment stressed blood cell; oxidative stress UV radiation blood

IT Fatigue, biological
(chronic fatigue syndrome, treatment of; inflammatory cytokine secretion inhibition with stressed blood cells)

IT Stress, animal
(heat; inflammatory cytokine secretion inhibition with stressed blood cells)

IT Anti-inflammatory agents
Antitumor agents
Blood cell
Inflammation
Mammalia
Oxidative stress, biological
UV C radiation
UV radiation
(inflammatory cytokine secretion inhibition with stressed blood cells)

IT Interleukin 6
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(inflammatory cytokine secretion inhibition with stressed blood cells)

IT Cytokines
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(inflammatory; inflammatory cytokine secretion inhibition with stressed blood cells)
IT Lymphoma
(inhibition of; inflammatory cytokine secretion inhibition with stressed blood cells)
IT Interferons
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(.gamma.; inflammatory cytokine secretion inhibition with stressed blood cells)
IT 10028-15-6, Ozone, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(stress with oxygen and; inflammatory cytokine secretion inhibition with stressed blood cells)
IT 7782-44-7, Oxygen, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(stress with ozone and; inflammatory cytokine secretion inhibition with stressed blood cells)

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L6 ANSWER 20 OF 22 USPATFULL on STN

DETD The present invention also relates to methods for the treatment of certain diseases and medical conditions (many of which can be characterized as **inflammatory** diseases) that are mediated by TNF, as well as the related sequela and symptoms associated therewith. A non-exclusive list of acute and chronic TNF-mediated diseases includes but is not limited to the following: cachexia/anorexia; cancer (e.g., leukemias); chronic **fatigue** syndrome; depression; diabetes (e.g., juvenile onset Type 1 and diabetes mellitus); fibromyelgia or analgesia; graft versus host rejection; hyperalgesia; **inflammatory** bowel disease; ischemic, including cerebral ischemia (brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration); lung diseases (e.g., adult respiratory distress syndrome and pulmonary fibrosis); multiple sclerosis; neuroinflammatory diseases; ocular diseases; pain; pancreatitis; pulmonary fibrosis; reperfusion injury; rheumatic diseases (e.g., rheumatoid arthritis, osteoarthritis, juvenile (rheumatoid) arthritis, seronegative polyarthritis, ankylosing spondylitis, Reiter's syndrome and reactive arthritis, psoriatic arthritis, enteropathic arthritis, polymyositis, dermatomyositis, scleroderma, systemic sclerosis, vasculitis, cerebral vasculitis, Lyme disease, staphylococcal-induced ("septic") arthritis, Sjogren's syndrome, rheumatic fever, polychondritis and polymyalgia rheumatica and giant cell arteritis); septic shock; side effects from **radiation** therapy; systemic lupus erythematous; temporal mandibular joint disease; thyroiditis; tissue transplantation or an **inflammatory** condition resulting from strain, sprain, cartilage damage, trauma, orthopedic surgery, infection or other disease process.

DETD In a specific embodiment, the present invention is directed to the use of a TNFbp product(s) in combination (pretreatment, post-treatment or concurrent treatment) with any of one or more interleukin-1 inhibitors for the treatment of TNF-mediated diseases, including acute and chronic inflammation such as cachexia/anorexia; chronic **fatigue** syndrome, depression; diabetes (e.g., juvenile onset Type 1 and diabetes mellitus); fibromyelgia or analgesia; graft versus host rejection; hyperalgesia, **inflammatory** bowel disease; ischemic injury, including cerebral ischemia (e.g., brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration); lung diseases (e.g., ARDS and pulmonary fibrosis); multiple sclerosis, ocular diseases; pain; pancreatitis, reperfusion injury; rheumatic diseases (e.g., rheumatoid arthritis, osteoarthritis, juvenile (rheumatoid) arthritis, seronegative polyarthritis, ankylosing spondylitis, Reiter's syndrome and reactive arthritis, psoriatic arthritis, enteropathic arthritis, polymyositis, dermatomyositis, scleroderma, systemic sclerosis, vasculitis, cerebral vasculitis, Lyme disease, staphylococcal-induced ("septic") arthritis, Sjogren's syndrome, rheumatic fever, polychondritis and polymyalgia rheumatica and giant cell arteritis); septic shock; side effects from **radiation** therapy; temporal mandibular joint disease; tumor metastasis; or an **inflammatory** condition resulting from strain, sprain, cartilage damage, trauma, orthopedic surgery, infection or other disease processes. Classes of interleukin-1 inhibitors include interleukin-1 receptor antagonists (any compound capable of specifically preventing activation of cellular receptors to IL-1) such as IL-1ra, as described below; anti-IL-1 receptor monoclonal antibodies (e.g., EP 623674), the disclosure of which is hereby incorporated by reference; IL-1 binding proteins such as soluble IL-1 receptors (e.g., U.S. Pat. Nos. 5,492,888, 5,488,032, and 5,464,

In an ongoing study commencing May of 1996, at the Hospitale El Mexico in San Jose, Costa Rica, patients who were documented as having cancers of various organ systems were **treated** with standard radiation and chemotherapeutic regimens, and were simultaneously given the dietary supplement of the present invention during the course of their oncological therapy. All of the patients' cancers were documented by accepted medical procedures including histological type and grade, appropriate TNM/Dukes staging by surgical evaluation and appropriate scans. Surgical excision, tumor debulking, resection and lymph node dissection and removal were carried out as dictated by the individual presentations. Radiation therapy where appropriate, was administered in accepted **dosages** in rads/m.sup.2 in divided **doses** utilizing Co 60. All chemotherapeutic agents were administered according to internationally accepted **dosage** guidelines of mg/m.sup.2 or mg/kg appropriate to the histological type and grade as well as the TNM class/Duke's classification/stage of the cancer. Appropriate blood counts and chemistries were obtained serially to monitor effects of systemic chemotherapy and **radiation** effects. Patients were also clinically monitored for secondary infections, weight loss, wasting, **fatigue** and other common side effects of chemo/radio therapy.

DETD Comments: Total body irradiation greater than 1000r in a single **dose** results in complete loss of bone marrow function, central nervous system toxicity, nausea, vomiting, diarrhea and death of the individual within 30 days from anemia, septicemia, encephalitis and carditis. By administering radiation in smaller frequent **doses** and shielding, we have been able to exceed this amount while **reducing** the incidence of lethal tissue damage. While bone marrow **suppression** and subsequent systemic infection from local irradiation is uncommon, tissue inflammation and latent scarring (**radiation** fibrosis) as well as **fatigue** are not.

PI US 5770217 19980623

L24 ANSWER 2 OF 42 CAPLUS COPYRIGHT 2003 ACS on STN

AB Participants of the Chernobyl clean-up (n = 145) teams exposed to radiation doses from 0.05 to 3.5 Gy who had for the first time complained of pathol. somatosensory sensations (ostealgic syndrome), 20 healthy subjects, and 50 veterans of the war in Afghanistan with posttraumatic stress disorder (PTSD) were examd. by a neuropsychiatrist and presented with the MMPI test. Somatosensory evoked potentials (SSEPs) were recorded. Paresthesia and cenesthopathy were characteristic of the participants of the Chernobyl clean-up. Sensation disorders of the cerebral type, kinesthetic illusions, cenesthopathic hypochondriac disorders, and paroxysmal psychosensory states predominated in this group of subjects. They differed significantly from the veterans with PTSD in markedly increased scores on MMPI scales (hypochondriasis, schizophrenia, pure hypochondriasis, pure schizophrenia, emotional exclusion, and perception oddity), which closely correlated with clin. somatosensory symptoms. In clean-up workers, somatosensory disorders were significantly assocd. with hypochondriac and schizophrenic-like symptoms. The latencies (LPs) of main SSEP components-N20, P25, N140, P300, and N400-were increased and their amplitudes decreased in subjects exposed to radiation. Their SSEPs had significant topog. deviations in the left temporoparietal area: the contralateral LPs were increased, whereas the contralateral amplitudes of the thalamocortical N20 component and the cortical P25 component were decreased as compared to normal values. Somatosensory disorders and hypochondriac and schizophrenic symptoms were significantly correlated with changes in the SSEPs. The decrease in the N20 amplitude and increase in the P25 latency in the left temporoparietal area were **dose**-dependent. The results suggest cerebral rather than peripheral origin of ostealgic syndrome and other somatosensory disorders in the participants of the Chernobyl clean-up. These disorders are assocd. with radiation-induced dysfunction of the corticolimbic structures of the left-dominant-hemisphere. It is suggested that somatosensory disorders in patients exposed to low **doses** of **radiation** can be considered as manifestations of chronic **fatigue** syndrome /fibromyalgia, whereas schizoform org. brain lesions manifest themselves after exposure to a **radiation dose** of 0.3-0.5 Gy.

AN 2003:54195 CAPLUS

DN 139:18462

L26 ANSWER 7 OF 19 USPATFULL on STN

SUMM The current standard of medical care for **treating** prostate cancer includes radical or nerve-sparing prostatectomy in which the entire prostate gland is surgically removed, and brachytherapy in which radiation seeds at low **dose** are permanently implanted in the prostate gland radiating effectively for 6 to 9 months or radiation seeds at **high dose** are temporarily implanted in the prostate for about 2 days, combined with external-beam radiation therapy to catch microscopic cancer cells that may have penetrated or could penetrate the prostate capsule. Side effects from surgery include incontinence and impotence. The cancer recurrence rate after surgery can be as high as approximately 35% at 5 years, and approximately 60% at 10 years, particularly when the prostatic-specific antigen level (discussed below) is greater than 10. **Radiation** therapy has short-term side effects such as skin reactions, **fatigue** and nausea. Additional long-term side effects of **radiation** therapy to the prostate include urinary incontinence (loss of bladder **control**) and impotence, as well as damage to surrounding organs.

PI US 6477426 B1 20021105

L26 ANSWER 5 OF 19 USPATFULL on STN

SUMM [0031] The side effects of radiation are similar to those of chemotherapy and arise for the same reason, the damage of healthy tissue. Radiation is usually more localized than chemotherapy, but **treatment** is still accompanied by damage to previously healthy tissue. Many of the side effects are unpleasant, and radiation also shares with chemotherapy the disadvantage of being mutagenic, carcinogenic and teratogenic in its own right. While normal cells usually begin to recover from **treatment** within two hours of **treatment**, mutations may be induced in the genes of the healthy cells. These risks are elevated in certain tissues, such as those in the reproductive system. It has also been found that people tolerate radiation differently. **Doses** that may not lead to new cancers in one individual may in fact spawn additional cancers in another individual. This could be due to pre-existing mutations in cell cycle check proteins or repair enzymes, but current practice would not be able to predict at what **dose** a particular individual is at risk. Common side effects of **radiation** include: bladder irritation; **fatigue**; diarrhea; low blood counts; mouth irritation; taste alteration; loss of appetite; alopecia; skin irritation; change in pulmonary function; enteritis; sleep disorders; and others.

PI US 2003068307 A1 20030410

L6 ANSWER 22 OF 22 USPATFULL on STN

SUMM A disease or medical condition is considered to be an "interleukin-1 mediated disease" if the spontaneous or experimental disease or medical condition is associated with elevated levels of IL-1 in bodily fluids or tissue or if cells or tissues taken from the body produce elevated levels of IL-1 in culture. In many cases, such interleukin-1 mediated diseases are also recognized by the following additional two conditions: (1) pathological findings associated with the disease or medical condition can be mimicked experimentally in animals by the administration of IL-1; and (2) the pathology induced in experimental animal models of the disease or medical condition can be inhibited or abolished by treatment with agents which inhibit the action of IL-1. In most interleukin-1 mediated diseases at least two of the three conditions are met, and in many interleukin-1 mediated diseases all three conditions are met. A non-exclusive list of acute and chronic interleukin-1 (IL-1)-mediated **inflammatory** diseases includes but is not limited to the following: acute pancreatitis; ALS; Alzheimer's disease; cachexia/anorexia; asthma; atherosclerosis; chronic **fatigue** syndrome, fever; diabetes (e.g., insulin diabetes); glomerulonephritis; graft versus host rejection; hemohorragic shock; hyperalgesia, **inflammatory** bowel disease; **inflammatory** conditions of a joint, including osteoarthritis, psoriatic arthritis and rheumatoid arthritis; ischemic injury, including cerebral ischemia (e.g., brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration); lung diseases (e.g., ARDS); multiple myeloma; multiple sclerosis; myelogenous (e.g., AML and CML) and other leukemias; myopathies (e.g., muscle protein metabolism, esp. in sepsis); osteoporosis; Parkinson's disease; pain; pre-term labor; psoriasis; reperfusion injury; septic shock; side effects from **radiation** therapy, temporal mandibular joint disease, tumor metastasis; or an **inflammatory** condition resulting from strain, sprain, cartilage damage, trauma, orthopedic surgery, infection or other disease processes.

DETD In a specific embodiment, the present invention is directed to the use of an IL-1 inhibitor (e.g., preferably IL-1ra product and more preferably IL-1ra) in combination (pretreatment, post-treatment or concurrent treatment) with any of one or more **COX2** inhibitors, their prodrug esters or pharmaceutically acceptable salts thereof for the treatment of acute and chronic inflammation. Examples of **COX2** inhibitors, prodrug esters or pharmaceutically acceptable salts thereof include, for example, celecoxib. Structurally related **COX2** inhibitors having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

PI US 6096728 20000801

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doxorubicin (50 to 60 mg/m(square); and cyclophosphamide (500 to 600 mg/m(square).

DETD [0696] In one embodiment, a therapy for the treatment of superficial bladder cancer is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents.

DETD [0697] In another embodiment, a **combination** for the treatment of superficial bladder cancer is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents in **combination** with one or more of the following **combinations** of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; and 2) cisplatin, 5-fluorouracil. A **combination** of chemotherapeutic agents that can be used in **combination** with **radiation** therapy and a **COX-2** selective inhibiting agent and a DNA topoisomerase inhibitor is a **combination** of cisplatin, methotrexate, vinblastine.

DETD [0698] Currently no curative therapy exists for metastatic bladder cancer. The present invention contemplates an effective treatment of bladder cancer leading to improved tumor inhibition or regression, as compared to current therapies. In the treatment of metastatic bladder cancer, a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents can be used to treat the disease in **combination** with surgery, **radiation** therapy and/or with chemotherapeutic agents.

DETD [0699] In one embodiment a therapy for the treatment of metastatic bladder cancer is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents. In another embodiment, therapy for the treatment of metastatic bladder cancer is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents in **combination** with one or more of the following **combinations** of antineoplastic agents: 1) cisplatin and methotrexate; 2) doxorubicin, vinblastine, cyclophosphamide, and 5-fluorouracil; 3) vinblastine, doxorubicin, cisplatin, methotrexate; 4) vinblastine, cisplatin, methotrexate; 5) cyclophosphamide, doxorubicin, cisplatin; 6) 5-fluorouracil, cisplatin.

DETD [0703] In one embodiment, a therapy for the treatment of non-metastatic adenocarcinoma that may be used in the methods, **combinations** and compositions of the present invention include the use of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents along with preoperative biliary tract decompression (patients presenting with obstructive jaundice); surgical resection, including standard resection, extended or radial resection and distal pancreatectomy (tumors of body and tail); adjuvant **radiation**; and/or chemotherapy.

DETD [0704] In one embodiment for the treatment of metastatic adenocarcinoma, a therapy consists of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents of the present invention in **combination** with continuous treatment of 5-fluorouracil, followed by weekly cisplatin therapy.

DETD [0705] In another embodiment a **combination** therapy for the treatment of cystic neoplasms is the use of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents along with resection.

DETD [0708] Celomic epithelial carcinoma accounts for approximately 90% of ovarian cancer cases. In one embodiment, a therapy for the treatment of ovary cancer is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents.

DETD [0709] Single agents that can be used in **combination** with a **COX-2** selective inhibiting agent and a DNA

topoisomerase I inhibiting agents include, but are not limited to: alkylating agents, ifosfamide, cisplatin, carboplatin, taxol, doxorubicin, 5-fluorouracil, methotrexate, mitomycin, hexamethylmelamine, progestins, antiestrogens, prednimustine, dihydroxybusulfan, galactitol, interferon alpha, and interferon gamma.

DETD [0710] In another embodiment, **combinations** for the treatment of celomic epithelial carcinoma is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents in **combination** with one or more of the following **combinations** of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; 2) hexamthylmelamine, cyclophosphamide, doxorubicin, cisplatin; 3) cyclophosphamide, hexamehtylmelamine, 5-fluorouracil, cisplatin; 4) melphalan, hexamethylmelamine, cyclophosphamide; 5) melphalan, doxorubicin, cyclophosphamide; 6) cyclophosphamide, cisplatin, carboplatin; 7) cyclophosphamide, doxorubicin, hexamethylmelamine, cisplatin; 8) cyclophosphamide, doxorubicin, hexamethylmelamine, carboplatin; 9) cyclophosphamide, cisplatin; 10) hexamethylmelamine, doxorubicin, carboplatin; 11) cyclophosphamide, hexamethlmelamine, doxorubicin, cisplatin; 12) carboplatin, cyclophosphamide; 13) cisplatin, cyclophosphamide.

DETD [0712] In one embodiment, a therapy for the treatment of germ cell carcinoma is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents.

DETD [0713] In another embodiment, a therapy for the treatment of germ cell carcinoma is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents in **combination** with one or more of the following **combinations** of antineoplastic agents: 1) vincristine, actinomycin D, cyclophosphamide; 2) bleomycin, etoposide, cisplatin; 3) vinblastine, bleomycin, cisplatin.

DETD [0715] In one embodiment, a therapy for the treatment of fallopian tube cancer is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents.

DETD [0716] In another embodiment, a therapy for the treatment of fallopian tube cancer is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents in **combination** with on or more of the following of antineoplastic agents: alkylating agents, ifosfamide, cisplatin, carboplatin, taxol, doxorubicin, 5-fluorouracil, methotrexate, mitomycin, hexamethylmelamine, progestins, antiestrogens, prednimustine, dihydroxybusulfan, galactitol, interferon alpha, and interferon gamma.

DETD [0717] In still another embodiment, therapy for the treatment of fallopian tube cancer is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents in **combination** with one or more of the following **combinations** of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; 2) hexamthylmelamine, cyclophosphamide, doxorubicin, cisplatin; 3) cyclophosphamide, hexamehtylmelamine, 5-fluorouracil, cisplatin; 4) melphalan, hexamethylmelamine, cyclophosphamide; 5) melphalan, doxorubicin, cyclophosphamide; 6) cyclophosphamide, cisplatin, carboplatin; 7) cyclophosphamide, doxorubicin, hexamethylmelamine, cisplatin; 8) cyclophosphamide, doxorubicin, hexamethylmelamine, carboplatin; 9) cyclophosphamide, cisplatin; 10) hexamethylmelamine, doxorubicin, carboplatin; 11) cyclophosphamide, hexamethlmelamine, doxorubicin, cisplatin; 12) carboplatin, cyclophosphamide; 13) cisplatin, cyclophosphamide.

DETD [0721] In one embodiment, a therapy for the treatment of central nervous system cancers is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting

agent and a DNA topoisomerase I inhibiting agents.

DETD [0722] In another embodiment, a therapy for the treatment of malignant glioma is a **combination** of neoplasia disorder effective amounts of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents in **combination** with one or more of the following **combinations** of therapies and antineoplastic agents:: 1) **radiation** therapy, BCNU (carmustine); 2) **radiation** therapy, methyl CCNU (lomustine); 3) **radiation** therapy, medol; 4) **radiation** therapy, procarbazine; 5) **radiation** therapy, BCNU, medrol; 6) hyperfraction **radiation** therapy, BCNU; 7) **radiation** therapy, misonidazole, BCNU; 8) **radiation** therapy, streptozotocin; 9) **radiation** therapy, BCNU, procarbazine; 10) **radiation** therapy, BCNU, hydroxyurea, procarbazine, VM-26; 11) **radiation** therapy, BNCU, 5-flourouacil; 12) **radiation** therapy, Methyl CCNU, dacarbazine; 13) **radiation** therapy, misonidazole, BCNU; 14) diaziquone; 15) **radiation** therapy, PCNU; 16) procarbazine (matulane), CCNU, vincristine. A dose of **radiation** therapy is about 5,500 to about 6,000 cGY. Radiosensitizers include misonidazole, intra-arterial Budr and intravenous iododeoxyuridine (IUdR). It is also contemplated that radiosurgery may be used in **combinations** with a **COX-2** selective inhibiting agent and an DNA topoisomerase I inhibiting agents.

DETD [0724] Table Nos. 22 and 23 provide additional non-limiting illustrative examples of **combination** therapies that can be used in the methods, **combinations** and compositions of the present invention. In each **combination** identified in Table Nos. 22 and 23, the individual **combination** is used in **combination** with an aromatase inhibiting agent. Exemplary aromatase inhibiting agents that can be used in the below non-limiting illustrative examples include anastrozole, atamestane, exemestane, fadrozole, finrozol, formestane, letrozole, minamestane, MR-20492, Testolactone, YM-511, and vorozole. Other examples of aromatase inhibiting agents that can be used in the **combinations** of the below examples are provided in Table No. 3, above. Additionally, non-limiting illustrative examples of **combinations** of **COX-2** selective inhibiting agents and aromatase inhibiting agents are provided in Table No. 24 below. Table No. 22 provides non-limiting illustrative examples of a **COX-2** selective inhibiting agent in **combination** with a single antineoplastic agent in the treatment of an illustrative neoplasia disorder. Table No. 23 provides non-limiting illustrative examples of a **COX-2** selective inhibiting agent in **combination** with multiple antineoplastic agents in the treatment of an illustrative neoplasia disorder.

TABLE 22

A **COX-2** Inhibiting Agent in **Combination** with a Single Antineoplastic Agent.

COX-2 Inhibitor	Antineoplastic Agents	Indication
Celecoxib	Anastrozole	Breast
Celecoxib	Capecitabine	Breast
Celecoxib	Docetaxel	Breast
Celecoxib	Gemcitabine	Breast, Pancreas
Celecoxib	Letrozole	Breast
Celecoxib	Megestrol	Breast
Celecoxib	Paclitaxel	Breast
Celecoxib	Tamoxifen	Breast
Celecoxib	Toremifene	Breast

Celecoxib	Vinorelbine	Breast, Lung
Celecoxib	Topotecan	Lung
Celecoxib	Etoposide	Lung
Celecoxib	Fluorouracil	Colon
Celecoxib	Irinotecan (CPT-11)	Colon, Bladder
Celecoxib	Retinoids	Colon
Celecoxib	DFMO	Colon
Celecoxib	Ursodeoxycholic acid	Colon
Celecoxib	Calcium carbonate	Colon
Celecoxib	Selenium	Colon
Celecoxib	Sulindac sulfone	Colon
Celecoxib	Carboplatin	Brain
Celecoxib	Goserelin Acetate	Prostate
Celecoxib	Cisplatin	Lung
Celecoxib	Ketoconazole	Prostate
Rofecoxib	Anastrozole	Breast
Rofecoxib	Capecitabine	Breast
Rofecoxib	Docetaxel	Breast
Rofecoxib	Gemcitabine	Breast, Pancreas
Rofecoxib	Letrozole	Breast
Rofecoxib	Megestrol	Breast
Rofecoxib	Paclitaxel	Breast
Rofecoxib	Tamoxifen	Breast
Rofecoxib	Toremifene	Breast
Rofecoxib	Vinorelbine	Breast, Lung
Rofecoxib	Irinotecan (CPT-11)	Colon, Bladder
Rofecoxib	Retinoids	Colon
Rofecoxib	DFMO	Colon
Rofecoxib	Ursodeoxycholic acid	Colon
Rofecoxib	Calcium carbonate	Colon
Rofecoxib	Selenium	Colon
Rofecoxib	Sulindac sulfone	Colon
Rofecoxib	Carboplatin	Brain
Rofecoxib	Goserelin Acetate	Prostate
Rofecoxib	Cisplatin	Lung
Rofecoxib	Ketoconazole	Prostate
Valdecoxib	Anastrozole	Breast
Valdecoxib	Capecitabine	Breast
Valdecoxib	Docetaxel	Breast
Valdecoxib	Gemcitabine	Breast, Pancreas
Valdecoxib	Letrozole	Breast
Valdecoxib	Megestrol	Breast
Valdecoxib	Paclitaxel	Breast
Valdecoxib	Tamoxifen	Breast
Valdecoxib	Toremifene	Breast
Valdecoxib	Vinorelbine	Breast, Lung
Valdecoxib	Topotecan	Lung
Valdecoxib	Etoposide	Lung
Valdecoxib	Fluorouracil	Colon
Valdecoxib	Irinotecan (CPT-11)	Colon, Bladder
Valdecoxib	Retinoids	Colon
Valdecoxib	DFMO	Colon
Valdecoxib	Ursodeoxycholic acid	Colon
Valdecoxib	Calcium carbonate	Colon
Valdecoxib	Selenium	Colon
Valdecoxib	Sulindac sulfone	Colon
Valdecoxib	Carboplatin	Brain
Valdecoxib	Goserelin Acetate	Prostate
Valdecoxib	Cisplatin	Lung
Valdecoxib	Ketoconazole	Prostate
Deracoxib	Anastrozole	Breast
Deracoxib	Capecitabine	Breast
Deracoxib	Docetaxel	Breast
Deracoxib	Gemcitabine	Breast, Pancreas

Deracoxib	Letrozole	Breast
Deracoxib	Megestrol	Breast
Deracoxib	Paclitaxel	Breast
Deracoxib	Tamoxifen	Breast
Deracoxib	Toremifene	Breast
Deracoxib	Vinorelbine	Breast, Lung
Deracoxib	Topotecan	Lung
Deracoxib	Etoposide	Lung
Deracoxib	Fluorouracil	Colon
Deracoxib	Irinotecan (CPT-11)	Colon, Bladder
Deracoxib	Retinoids	Colon
Deracoxib	DFMO	Colon
Deracoxib	Ursodeoxycholic acid	Colon
Deracoxib	Calcium carbonate	Colon
Deracoxib	Selenium	Colon
Deracoxib	Sulindac sulfone	Colon
Deracoxib	Carboplatin	Brain
Deracoxib	Goserelin Acetate	Prostate
Deracoxib	Cisplatin	Lung
Deracoxib	Ketoconazole	Prostate
JTE-522	Anastrozole	Breast
JTE-522	Capecitabine	Breast
JTE-522	Docetaxel	Breast
JTE-522	Gemcitabine	Breast, Pancreas
JTE-522	Letrozole	Breast
JTE-522	Megestrol	Breast
JTE-522	Paclitaxel	Breast
JTE-522	Tamoxifen	Breast
JTE-522	Toremifene	Breast
JTE-522	Vinorelbine	Breast, Lung
JTE-522	Topotecan	Lung
JTE-522	Etoposide	Lung
JTE-522	Fluorouracil	Colon
JTE-522	Irinotecan (CPT-11)	Colon, Bladder
JTE-522	Retinoids	Colon
JTE-522	DFMO	Colon
JTE-522	Ursodeoxycholic acid	Colon
JTE-522	Calcium carbonate	Colon
JTE-522	Selenium	Colon
JTE-522	Sulindac sulfone	Colon
JTE-522	Carboplatin	Brain
JTE-522	Goserelin Acetate	Prostate
JTE-522	Cisplatin	Lung
JTE-522	Ketoconazole	Prostate
MK-663	Anastrozole	Breast
MK-663	Capecitabine	Breast
MK-663	Docetaxel	Breast
MK-663	Gemcitabine	Breast, Pancreas
MK-663	Letrozole	Breast
MK-663	Megestrol	Breast
MK-663	Paclitaxel	Breast
MK-663	Tamoxifen	Breast
MK-663	Toremifene	Breast
MK-663	Vinorelbine	Breast, Lung
MK-663	Topotecan	Lung
MK-663	Etoposide	Lung
MK-663	Fluorouracil	Colon
MK-663	Irinotecan (CPT-11)	Colon, Bladder
MK-663	Retinoids	Colon
MK-663	DFMO	Colon
MK-663	Ursodeoxycholic acid	Colon
MK-663	Calcium carbonate	Colon
MK-663	Selenium	Colon
MK-663	Sulindac sulfone	Colon

MK-663	Carboplatin	Brain
MK-663	Goserelin Acetate	Prostate
MK-663	Cisplatin	Lung
MK-663	Ketoconazole	Prostate

DETD [0725]
TABLE 23

A **COX-2** Inhibiting Agent in **Combination** with Multiple Antineoplastic Agents.

COX-2 Inhibitor	Antineoplastic Agents	Indication
Celecoxib	Doxorubicin and Cyclophosphamide	Breast
Celecoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Celecoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Celecoxib	Mitoxantrone, Fluorouracil and Leucovorin	Breast
Celecoxib	Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
Celecoxib	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Celecoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Celecoxib	Vinbiastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
Celecoxib	Fluorouracil, Levamisole	Colon
Celecoxib	Leucovorin, Fluorouracil	Colon
Celecoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Celecoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Celecoxib	Etoposide, Carboplatin	Lung
Celecoxib	Etoposide, Cisplatin	Lung
Celecoxib	Paclitaxel, Carboplatin	Lung
Celecoxib	Gemcitabine, Cisplatin	Lung
Celecoxib	Paclitaxel, Cisplatin	Lung
Rofecoxib	Doxorubicin and Cyclophosphamide	Breast
Rofecoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Rofecoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Rofecoxib	Mitoxantrone, Flourouracil and Leucovorin	Breast
Rofecoxib	Vinbiastine, Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
Rofecoxib	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Rofecoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Rofecoxib	Vinblastine, Doxorubicin,	Breast

	Thiotepa, Fluoxymesterone	
Rofecoxib	Fluorouracil, Levamisole	Colon
Rofecoxib	Leucovorin, Fluorouracil	Colon
Rofecoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Rofecoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Rofecoxib	Etoposide, Carboplatin	Lung
Rofecoxib	Etoposide, Cisplatin	Lung
Rofecoxib	Paclitaxel, Carboplatin	Lung
Rofecoxib	Gemcitabine, Cisplatin	Lung
Rofecoxib	Paclitaxel, Cisplatin	Lung
Valdecoxib	Doxorubicin and Cyclophosphamide	Breast
Valdecoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Valdecoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Valdecoxib	Mitoxantrone, Fluorouracil and Leucovorin	Breast
Valdecoxib	Vinbiastine, Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
Valdecoxib	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Valdecoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Valdecoxib	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
Valdecoxib	Fluorouracil, Levamisole	Colon
Valdecoxib	Leucovorin, Fluorouracil	Colon
Valdecoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Valdecoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Valdecoxib	Etoposide, Carboplatin	Lung
Valdecoxib	Etoposide, Cisplatin	Lung
Valdecoxib	Paclitaxel, Carboplatin	Lung
Valdecoxib	Gemcitabine, Cisplatin	Lung
Valdecoxib	Paclitaxel, Cisplatin	Lung
Deracoxib	Doxorubicin and Cyclophosphamide	Breast
Deracoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Deracoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Deracoxib	Mitoxantrone, Fluorouracil and Leucovorin	Breast
Deracoxib	Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
Deracoxib	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Deracoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Deracoxib	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
Deracoxib	Fluorouracil, Levamisole	Colon

Deracoxib	Leucovorin, Fluorouracil	Colon
Deracoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Deracoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Deracoxib	Etoposide, Carboplatin	Lung
Deracoxib	Etoposide, Cisplatin	Lung
Deracoxib	Paditaxel, Carboplatin	Lung
Deracoxib	Gemcitabine, Cisplatin	Lung
Deracoxib	Paclitaxel, Cisplatin	Lung
JTE-522	Doxorubicin and Cyclophosphamide	Breast
JTE-522	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
JTF-522	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
JTE-522	Mitoxantrone, Flourouracil and Leucovorin	Breast
JTE-522	Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
JTE-522	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
JTE-522	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
JTE-522	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
JTE-522	Fluorouracil, Levaniisole	Colon
JTE-522	Leucovorin, Fluorouracil	Colon
JTE-522	Cyclophosphamide, Doxorubicin, Etoposide	Lung
JTE-522	Cyclophosphamide, Doxorubicin, Vincristine	Lung
JTE-522	Etoposide, Carboplatin	Lung
JTE-522	Etoposide, Cisplatin	Lung
JTE-522	Paclitaxel, Carboplatin	Lung
JTE-522	Gemcitabine, Cisplatin	Lung
JTE-522	Paclitaxel, Cisplatin	Lung
MK-663	Doxorubicin and Cyclophosphamide	Breast
MK-663	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
MK-663	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
MK-663	Mitoxantrone, Fluorouracil and Leucovorin	Breast
MK-663	Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
MK-663	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
MK-663	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
MK-663	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
MK-663	Fluorouracil, Levamisole	Colon
MK-663	Leucovorin, Fluorouracil	Colon
MK-663	Cyclophosphamide,	Lung

	Doxorubicin, Etoposide	
MK-663	Cyclophosphamide, Doxorubicin, Vincristine	Lung
MK-663	Etoposide, Carboplatin	Lung
MK-663	Etoposide, Cisplatin	Lung
MK-663	Pacitaxel, Carboplatin	Lung
MK-663	Gemcitabine, Cisplatin	Lung
MK-663	Paclitaxel, Cisplatin	Lung
MK-663	Doxorubicin and Cyclophosphamide	Breast
MK-663	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
MK-663	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
MK-663	Mitoxantrone, Fluorouracil and Leucovorin	Breast
MK-663	Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
MK-663	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
MK-663	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
MK-663	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
MK-663	Fluorouracil, Levamisole	Colon
MK-663	Leucovorin, Fluorouracil	Colon
MK-663	Cyclophosphamide, Doxorubicin, Etoposide	Lung
MK-663	Cyclophosphamide, Doxorubicin, Vincristine	Lung
MK-663	Etoposide, Carboplatin	Lung
MK-663	Etoposide, Cisplatin	Lung
MK-663	Paclitaxel, Carboplatin	Lung
MK-663	Gemcitabine, Cisplatin	Lung
MK-663	Paclitaxel, Cisplatin	Lung

DETD [0727] Table No. 24 illustrates examples of some **combinations** of the present invention where the **combination** comprises a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agent.

TABLE 24

Combinations of **COX-2** selective inhibiting agents and DNA topoisomerase I inhibiting agents

COX-2 selective inhibiting agent	DNA topoisomerase I inhibiting agent
Celecoxib	irinotecan
Rofecoxib	irinotecan
Valdecoxib	irinotecan
Deracoxib	irinotecan
JTE-522	irinotecan
MK-663	irmotecan
Celecoxib	camptothecin
Rofecoxib	camptothecin
Valdecoxib	camptothecin
Deracoxib	camptothecin
JTE-522	camptothecin
MK-663	camptothecin

Celecoxib lurtotecan
Rofecoxib lurtotecan
Valdecoxib lurtotecan
Deracoxib lurtotecan
JTE-522 lurtotecan
MK-663 lurtotecan
Celecoxib homosilatecans
Rofecoxib homosilatecans
Valdecoxib homosilatecans
Deracoxib homosilatecans
JTE-522 homosilatecans
MK-663 homosilatecans
Celecoxib 9-amino camptothecin
Rofecoxib 9-amino camptothecin
Valdecoxib 9-amino camptothecin
Deracoxib 9-amino camptothecin
JTE-522 9-amino camptothecin
MK-663 9-amino camptothecin
Celecoxib 9-nitrocamptothecin
Rofecoxib 9-nitrocamptothecin
Valdecoxib 9-nitrocamptothecin
Deracoxib 9-nitrocamptothecin
JTE-522 9-nitrocamptothecin
MK-663 9-nitrocamptothecin
Celecoxib 4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-
Rofecoxib 4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-
Valdecoxib 4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-
Deracoxib 4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-
JTE-522 4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-
MK-663 4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-
Celecoxib 4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride
Rofecoxib 4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride
Valdecoxib 4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride
Deracoxib 4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride
JTE-522 4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride
MK-663 4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydro chloride
Celecoxib topotecan
Rofecoxib topotecan
Valdecoxib topotecan
Deracoxib topotecan
JTE-522 topotecan
MK-663 topotecan
Celecoxib topotecan hydrochloride
Rofecoxib topotecan hydrochloride
Valdecoxib topotecan hydrochloride
Deracoxib topotecan hydrochloride
JTE-522 topotecan hydrochloride
MK-663 topotecan hydrochloride

DETD [0728] Evaluation of COX-1 and **COX-2** Activity in vitro

DETD [0729] The **COX-2** selective inhibiting agents of this invention exhibit inhibition in vitro of **COX-2**. The **COX-2** inhibition activity of the compounds illustrated in the Examples above were determined by the following methods. The **COX-2** inhibition activity of the other cyclooxygease-2 inhibitors of the present invention may also be determined by the following methods.

DETD [0731] Recombinant COX -1 and **COX-2** were prepared as

described by Gierse et al, [J. Biochem., 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine **COX-2** was cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and **COX-2** in a manner similar to the method of D. R. O'Reilly et al (Baculovirus Expression Vectors: A Laboratory Manual (1992)). Recombinant baculoviruses were isolated by transfecting 4 .mu.g of baculovirus transfer vector DNA into SF9 insect cells (2.times.108) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M. D. Summers and G. E. Smith, A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer (107-108 pfu/mL) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5.times.106/mL) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000.times.G for 30 minutes, and the resultant supernatant was stored at -80.degree. C. before being assayed for COX activity.

DETD [0732] b. Assay for COX-1 and **COX-2** activity

DETD [0734] c. Fast assay for COX-1 and **COX-2** activity

DETD [0735] COX activity was assayed as PGE2 formed/.mu.g protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (0.05 M Potassium phosphate, pH 7.5, 2 .mu.M phenol, 1 .mu.M heme, 300 .mu.M epinephrine) with the addition of 20 .mu.l of 100 .mu.M arachidonic acid (10 .mu.M). Compounds were pre-incubated with the enzyme for 10 minutes at 25.degree. C. prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after two minutes at 37.degree. C./room temperature by transferring 40 .mu.l of reaction mix into 160 .mu.l ELISA buffer and 25 .mu.M indomethacin. The PGE2 formed was measured by standard ELISA technology (Cayman Chemical). Results are shown below in Table 25.

TABLE 25

Example	**COX-2*** IC.sub.50 .mu.M	COX-1* IC.sub.50 .mu.M
1	0.7	43
2	>0.1	16.7
3	<0.1	64.4
4	<0.1	20.5
5	<0.1	18.8
6	<0.1	6.7
7	0.7	>500
8	<0.1	1.6
9	0.9	1.0
10	<0.1	1.5
11	<0.1	0.7
12	0.6	>500
13	0.2	>100
14	0.2	9.7
15	3.6	57
16	<0.1	94.6
17	<0.1	1.6
18	<0.1	5.6
19	<0.1	1.4

20	<0.1	2.8
21	0.8	>100
22	0.4	>100
23	<0.1	365
24	<0.1	0.2

* fast assay

DETD [0737] A **combination** therapy of a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents for the treatment or prevention of a neoplasia disorder in a mammal can be evaluated as described in the following tests.

DETD [0747] Solitary tumors are generated in the right hind legs of mice by the injection of 3.times.10.sup.5 viable NFSA tumor cells. Treatment with a **COX-2** selective inhibiting agent (6 mg/kg body weight) and a DNA topoisomerase I inhibiting agents or vehicle (0.05% Tween 20 and 0.95% polyethylene glycol) given in the drinking water is started when tumors are approximately 6 mm in diameter and the treatment ia continued for 10 consecutive days. Water bottles are changed every 3 days. In some experiments, tumor irradiation is performed 3-8 days after initiation of the treatment. The end points of the treatment are tumor growth delay (days) and TCD.sub.50 (tumor control dose 50, defined as the **radiation** dose yielding local tumor cure in 50% of irradiated mice 120 days after irradiation). To obtain tumor growth curves, three mutually orthogonal diameters of tumors are measured daily with a vernier caliper, and the mean values are calculated.

DETD [0748] Local tumor irradiation with single .gamma.-ray doses of 30, 40, or 50 Gy is given when these tumors reach 8 mm in diameter. Irradiation to the tumor is delivered from a dual-source .sup.137Cs irradiator at a dose rate of 6.31 Gy/minute. During irradiation, unanesthetized mice are immobilized on a jig and the tumor is centered in a circular **radiation** field 3 cm in diameter. Regression and regrowth of tumors is followed at 1-3 day intervals until the tumor diameter reaches approximately 14 mm.

DETD [0749] The magnitude of tumor growth delay as a function of **radiation** dose with or without treatment with a **COX-2** selective inhibiting agent and a DNA topoisomerase I inhibiting agents is plotted to determine the enhancement of tumor response to **radiation**. This requires that tumor growth delay after **radiation** be expressed only as the absolute tumor growth delay, i.e., the time in days for tumors treated with **radiation** to grow from 8 to 12 mm in diameter minus the time in days for untreated tumors to reach the same size. It also requires that the effect of the combined a **COX-2** selective inhibiting agent and DNA topoisomerase I inhibiting agents plus-**radiation** treatment be expressed as the normalized tumor growth delay. Normalized tumor growth delay is defined as the time for tumors treated with both a **COX-2** selective inhibiting agent and **radiation** to grow from 8 to 12 mm in diameter minus the time in days for tumors treated with a **COX-2** selective inhibiting agent and DNA topoisomerase I inhibiting agents alone to reach the same size.

DETD [0751] While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the active agents used in the methods, **combinations** and compositions of the present invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of

administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

CLM What is claimed is:

1. A method for treating, preventing or reducing the risk of developing a neoplasia disorder in a mammal in need thereof, comprising administering to the mammal in a **combination** therapy an amount of a DNA topoisomerase I inhibiting agent and an amount of a selective **COX-2** inhibiting agent wherein the amount of the DNA topoisomerase I inhibiting agent and the selective **COX-2** inhibiting agent together make a neoplasia disorder effective amount.

4. The method of claim 1 wherein the selective **COX-2** inhibiting agent is selected from compounds of Formula 1: ##STR60## or a pharmaceutically-acceptable salt or prodrug thereof, wherein A is a 5- or 6-member ring substituent selected from the group consisting of heterocyclyl and carbocyclyl, wherein A is optionally substituted with one or more radicals selected from the group consisting of hydroxy, alkyl, halo, oxo, and alkoxy; R.sup.1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein R.sup.1 is optionally substituted with one or more radicals selected from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio; R.sup.2 is selected from the group consisting of alkyl and amino; R.sup.3 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocycloalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-phenylaminoalkyl, N-phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl; and R.sup.4 is selected from the group consisting of hydrido and halo.

12. The method of claim 4 wherein the selective **COX-2** inhibiting agent is selected from the group consisting of rofecoxib, celecoxib, valdecoxib, deracoxib, etoricoxib, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine, 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide, 4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide, 3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone, N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide, 3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone, 4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide, 3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one, 4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide, 3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone, 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole, 4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-

yl)benzenesulfonamide, 4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide, 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide, 3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide, 3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide, 3-[(1-methyl-1H-imidazol-2-yl)thio]-4[(methylsulfonyl)amino]benzenesulfonamide, 5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone, N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide, 3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide, 1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]cyclopenten-1-yl]benzene, 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol 1-yl]benzenesulfonamide, 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine, 4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide, 4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide, 4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide, 4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide, [1,1':2',1"-terphenyl]-4-sulfonamide, 4-(methylsulfonyl)-1,1',2],1"-terphenyl, 4-(2-phenyl-3-pyridinyl)benzenesulfonamide, N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, and N-(4-nitro-2-phenoxyphenyl)methanesulfonamide.

13. The method of claim 12 wherein the selective **COX-2** inhibiting agent is rofecoxib.

14. The method of claim 12 wherein the selective **COX-2** inhibiting agent is celecoxib.

15. The method of claim 12 wherein the selective **COX-2** inhibiting agent is valdecoxib.

16. The method of claim 12 wherein the selective **COX-2** inhibiting agent is deracoxib.

17. The method of claim 12 wherein the selective **COX-2** inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide.

18. The method of claim 12 wherein the selective **COX-2** inhibiting agent is etoricoxib.

19. The method of claim 1 wherein the selective **COX-2** inhibiting agent is selected from compounds of Formula 2: ##STR61## or an isomer or pharmaceutically-acceptable salt or prodrug thereof, wherein X is selected from the group consisting of O, S and NR.sup.a; R.sup.a is alkyl; R is selected from the group consisting of carboxyl, alkyl, aralkyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl; R.sup.11 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein aryl is optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and R.sup.5 is one or more radicals independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl,

aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl, wherein R.sup.5 together with ring D optionally forms a naphthyl radical.

30. The method of claim 19 wherein the selective **COX-2** inhibiting agent is selected from the group consisting of 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid, 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid, 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid, and 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

31. The method of claim 1 wherein the selective **COX-2** inhibiting agent is selected from compounds of Formula 3: ##STR62## or an isomer or pharmaceutically-acceptable salt or prodrug thereof, wherein X is selected from the group consisting of O and S; R.sup.6 is

lower haloalkyl; R.sup.7 is selected from the group consisting of hydrido and halo; R.sup.8 is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, and 5- or 6-membered nitrogen containing heterocyclosulfonyl; R.sup.9 is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and R.sup.10 is selected from the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl.

37. The method of claim 31 wherein the selective **COX-2** inhibiting agent is selected from the group consisting of 6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, (S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, 6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, 7-(1,1-Dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,7-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 5,6-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 2,6-Bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 5,6,7-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,7,8-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, 6-Bromo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, 6-Chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid, and 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

38. The method of claim 37 wherein the selective **COX-2** inhibiting agent is selected from the group consisting of 6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, (S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, and 6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid.

39. The method of claim 1 wherein the selective **COX-2** inhibiting agent is selected from compounds that correspond in structure, and pharmaceutically acceptable salts thereof, of the group consisting of: N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-

2-yl]methyl]-3(2H)-pyridazinone, N-(4-nitro-2-phenoxyphenyl)methanesulfonamide, 3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone, N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide, 3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide, 3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide, 3-[(1-methyl-1H-imidazol-2-yl)thio]-4[(methylsulfonyl)amino]benzenesulfonamide, 5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone, N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide, 3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide, N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide.

42. The method of claim 1 wherein the selective **COX-2** inhibiting agent and the DNA topoisomerase I inhibiting agent are formulated in a single composition.

43. The method of claim 1 wherein the selective **COX-2** inhibiting agent and the DNA topoisomerase I inhibiting agent are provided as a separate component of a kit.

45. The method of claim 1 wherein the selective **COX-2** inhibiting agent and the DNA topoisomerase I inhibiting agent are administered in a sequential manner.

46. The method of claim 1 wherein the selective **COX-2** inhibiting agent and the DNA topoisomerase I inhibiting agent are administered in a substantially simultaneous manner.

47. A pharmaceutical composition comprising a DNA topoisomerase I inhibiting agent and a **COX-2** inhibiting agent wherein the DNA topoisomerase I inhibiting agent and the selective **COX-2** inhibiting agent together make a neoplasia disorder effective amount.

50. The pharmaceutical composition of claim 47 wherein the selective **COX-2** inhibiting agent is selected from compounds of Formula 1: ##STR63## or a pharmaceutically-acceptable salt or prodrug thereof, wherein A is a 5- or 6-member ring substituent selected from the group consisting of heterocyclyl and carbocyclyl, wherein A is optionally substituted with one or more radicals selected from the group consisting of hydroxy, alkyl, halo, oxo, and alkoxy; R.sup.1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein R.sup.1 is optionally substituted with one or more radicals selected from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio; R.sup.2 is selected from the group consisting of alkyl and amino; R.sup.3 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocycloalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, aminoalkyl,

alkylaminoalkyl, N-phenylaminoalkyl, N-phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl; and R.sup.4is selected from the group consisting of hydrido and halo.

58. The pharmaceutical composition of claim 50 wherein the selective **COX-2** inhibiting agent is selected from the group consisting of rofecoxib, celecoxib, valdecoxib, deracoxib, etoricoxib, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine, 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide, 4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide, 3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone, N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide, 3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone, 4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide, 3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one, 4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide, 3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone, 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole, 4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide, 4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide, 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide, 3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide, 3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide, 3-[(1-methyl-1H-imidazol-2-yl)thio]-4[(methylsulfonyl)amino]benzenesulfonamide, 5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone, N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide, 3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide, 1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]cyclopenten-1-yl]benzene, 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine, 4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide, 4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide, 4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide, 4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide, [1,1':2',1"-terphenyl]-4-sulfonamide, 4-(methylsulfonyl)-1,1',2],1"-terphenyl, 4-(2-phenyl-3-pyridinyl)benzenesulfonamide, N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, and N-(4-nitro-2-phenoxyphenyl)methanesulfonamide.

59. The pharmaceutical composition of claim 58 wherein the selective **COX-2** inhibiting agent is rofecoxib.

60. The pharmaceutical composition of claim 58 wherein the selective **COX-2** inhibiting agent is celecoxib.

61. The pharmaceutical composition of claim 58 wherein the selective **COX-2** inhibiting agent is valdecoxib.

62. The pharmaceutical composition of claim 58 wherein the selective **COX-2** inhibiting agent is deracoxib.

63. The pharmaceutical composition of claim 58 wherein the selective COX-2 inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide.

64. The pharmaceutical composition of claim 58 wherein the selective COX-2 inhibiting agent is etoricoxib.

65. The pharmaceutical composition of claim 50 wherein the selective COX-2 inhibiting agent is selected from compounds of Formula 2: ##STR64## or an isomer or pharmaceutically-acceptable salt or prodrug thereof, wherein X is selected from the group consisting of O, S and NR.sup.a; R.sup.a is alkyl; R is selected from the group consisting of carboxyl, alkyl, aralkyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl; R.sup.11 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein aryl is optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and R.sup.5 is one or more radicals independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl, wherein R.sup.5 together with ring D optionally forms a naphthyl radical.

76. The pharmaceutical composition of claim 65 wherein the selective COX-2 inhibiting agent is selected from the group consisting of 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid, 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid, 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(dimethylamino)sulfonyl]-2-

trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid, and 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

77. The pharmaceutical composition of claim 47 wherein the selective **COX-2** inhibiting agent is selected from compounds of Formula 3: ##STR65## or an isomer or pharmaceutically-acceptable salt or prodrug thereof, wherein X is selected from the group consisting of O and S; R.sup.6 is lower haloalkyl; R.sup.7 is selected from the group consisting of hydrido and halo; R.sup.8 is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, and 5- or 6-membered nitrogen containing heterocyclosulfonyl; R.sup.9 is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and R.sup.10 is selected from the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl.

83. The pharmaceutical composition of claim 77 wherein the selective **COX-2** inhibiting agent is selected from the group consisting of 6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, (S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, 6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, 7-(1,1-Dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,7-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 5,6-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 2,6-Bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 5,6,7-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,7,8-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, 6-Bromo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, 6-Chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid, and 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-

carboxylic acid.

84. The pharmaceutical composition of claim 83 wherein the selective **COX-2** inhibiting agent is selected from the group consisting of 6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, (S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, and 6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid.

85. The pharmaceutical composition of claim 47 wherein the selective **COX-2** inhibiting agent is selected from compounds that correspond in structure, and pharmaceutically acceptable salts thereof, of the group consisting of: N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, N-(4-nitro-2-phenoxyphenyl)methanesulfonamide, 3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone, N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide, 3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide, 3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide, 3-[(1-methyl-1H-imidazol-2-yl)thio]-4[(methylsulfonyl)amino]benzenesulfonamide, 5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone, N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide, 3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide, N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide.

91. The pharmaceutical composition of claim 47 wherein the selective **COX-2** inhibiting agent is present in an amount from about 0.1 mg to about 10,000 mg.

93. Use of a composition in preparation of a medicament useful in treating, preventing or lowering the risk of developing a neoplasia disorder in a mammal in need thereof, the composition comprising an amount of a DNA topoisomerase I inhibiting agent and an amount of a **COX-2** inhibiting agent wherein the amount of the DNA topoisomerase I inhibiting agent and the selective **COX-2** inhibiting agent together make a neoplasia disorder effective amount.

96. The use of claim 93 wherein the selective **COX-2** inhibiting agent is selected from compounds of Formula 1: ##STR66## or a pharmaceutically-acceptable salt or prodrug thereof, wherein A is a 5- or 6-member ring substituent selected from the group consisting of heterocyclyl and carbocyclyl, wherein A is optionally substituted with one or more radicals selected from the group consisting of hydroxy, alkyl, halo, oxo, and alkoxy; R.sup.1 is selected from the group

consisting of cyclohexyl, pyridinyl, and phenyl, wherein R.sup.1 is optionally substituted with one or more radicals selected from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio; R.sup.2 is selected from the group consisting of alkyl and amino; R.sup.3 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocycloalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-phenylaminoalkyl, N-phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl; and R.sup.4 is selected from the group consisting of hydrido and halo.

104. The use of claim 96 wherein the selective **COX-2** inhibiting agent is selected from the group consisting of rofecoxib, celecoxib, valdecoxib, deracoxib, etoricoxib, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine, 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide, 4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide, 3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone, N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide, 3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone, 4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide, 3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one, 4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide, 3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone, 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole, 4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide, 4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide, 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide, 3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide, 3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide, 3-[(1-methyl-1H-imidazol-2-yl)thio]-4[(methylsulfonyl)amino]benzenesulfonamide, 5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone, N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide, 3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide, 1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]cyclopenten-1-yl]benzene, 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine, 4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide, 4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide, 4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide, 4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide, [1,1':2',1"-terphenyl]-4-sulfonamide, 4-(methylsulfonyl)-1,1',2],1"-terphenyl, 4-(2-phenyl-3-pyridinyl)benzenesulfonamide, N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-

benzisothiazol-5-yl)methanesulfonamide, N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, and N-(4-nitro-2-phenoxyphenyl)methanesulfonamide.

105. The use of claim 104 wherein the selective **COX-2** inhibiting agent is rofecoxib.

106. The use of claim 104 wherein the selective **COX-2** inhibiting agent is celecoxib.

107. The use of claim 104 wherein the selective **COX-2** inhibiting agent is valdecoxib.

108. The use of claim 104 wherein the selective **COX-2** inhibiting agent is deracoxib.

109. The use of claim 104 wherein the selective **COX-2** inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide.

110. The use of claim 104 wherein the selective **COX-2** inhibiting agent is etoricoxib.

111. The use of claim 93 wherein the selective **COX-2** inhibiting agent is selected from compounds of Formula 2: ##STR67## or an isomer or pharmaceutically-acceptable salt or prodrug thereof, wherein X is selected from the group consisting of O, S and NR.sup.a; R.sup.a is alkyl; R is selected from the group consisting of carboxyl, alkyl, aralkyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl; R.sup.11 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein aryl is optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and R.sup.5 is one or more radicals independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl, wherein R.sup.5 together with ring D optionally forms a naphthyl radical.

122. The use of claim 111 wherein the selective **COX-2** inhibiting agent is selected from the group consisting of 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid, 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-phenyl-2-trifluoromethyl-2H-1-

benzopyran-3-carboxylic acid, 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid, 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid, and 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

123. The use of claim 93 wherein the selective **COX-2** inhibiting agent is selected from compounds of Formula 3: ##STR68## or an isomer or pharmaceutically-acceptable salt or prodrug thereof, wherein X is selected from the group consisting of O and S; R.sup.6 is lower haloalkyl; R.sup.7 is selected from the group consisting of hydrido and halo; R.sup.8 is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, and 5- or 6-membered nitrogen containing heterocyclosulfonyl; R.sup.9 is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and R.sup.10 is selected from the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl.

129. The use of claim 123 wherein the selective **COX-2** inhibiting agent is selected from the group consisting of 6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Trifluoromethoxy-2-trifluoromethyl-2-1-benzopyran-3-carboxylic acid, 6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-

carboxylic acid, 6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, (S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, 6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, 7-(1,1-Dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,7-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 5,6-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 2,6-Bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 5,6,7-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,7,8-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, 6-Bromo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, 6-Chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid, and 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

130. The use of claim 129 wherein the selective **COX-2** inhibiting agent is selected from the group consisting of 6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, (S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, (S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, and 6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid.

131. The use of claim 93 wherein the selective **COX-2** inhibiting agent is selected from compounds that correspond in structure, and pharmaceutically acceptable salts thereof, of the group consisting of: N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, N-(4-nitro-2-phenoxyphenyl)methanesulfonamide, 3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone, N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide, 3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide, 3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide, 3-[(1-methyl-1H-imidazol-2-yl)thio]-4[(methylsulfonyl)amino]benzenesulfonamide, 5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone, N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide, 3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide, N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide.

134. The method of claim 93 wherein the selective **COX-2** inhibiting agent and the DNA topoisomerase I inhibiting agent are formulated in a single composition.

135. The use of claim 93 wherein the selective **COX-2** inhibiting agent and the DNA topoisomerase I inhibiting agent are provided as a separate component of a kit.

137. The use of claim 93 wherein the selective **COX-2** inhibiting agent and the DNA topoisomerase I inhibiting agent are administered in a sequential manner.

138. The use of claim 93 wherein the selective **COX-2** inhibiting agent and the DNA topoisomerase I inhibiting agent are administered in a substantially simultaneous manner.

139. A kit comprising a DNA topoisomerase I inhibiting agent and a selective **COX-2** inhibiting agent wherein the DNA topoisomerase I inhibiting agent and the selective **COX-2** inhibiting agent together make a neoplasia disorder effective amount.

140. A method for the prevention or treatment of DNA topoisomerase I inhibiting agent-related diarrhea in a subject in need of such prevention or treatment wherein the method comprises administering to the subject a diarrhea preventing or treating-effective amount of a source of a **COX-2** inhibitor, thereby preventing or treating the DNA topoisomerase I inhibiting agent-related diarrhea.

141. The method of claim 140 wherein the source of a **COX-2** inhibiting agent is a source of a **COX-2** selective inhibiting agent.

142. The method of claim 141 wherein the source of a **COX-2** selective inhibiting agent is a **COX-2** selective inhibiting agent.

143. The method of claim 142 wherein the **COX-2** selective inhibiting agent is selected from the group consisting of celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, meloxicam, and ABT-963.

144. The method of claim 142 wherein the **COX-2** selective inhibiting agent is celecoxib.

145. The method of claim 142 wherein the **COX-2** selective inhibiting agent is valdecoxib.

146. The method of claim 142 wherein the **COX-2** selective inhibiting agent is deracoxib.

147. The method of claim 142 wherein the **COX-2** selective inhibiting agent is rofecoxib.

148. The method of claim 142 wherein the **COX-2** selective inhibiting agent is etoricoxib.

149. The method of claim 142 wherein the **COX-2** selective inhibiting agent is meloxicam.

150. The method of claim 142 wherein the **COX-2** selective inhibiting agent is ABT-963.

151. The method of claim 142 wherein the **COX-2** selective inhibiting agent is a chromene **COX-2** selective inhibiting agent.

152. The method of claim 141 wherein the source of a **COX-**

2 selective inhibiting agent is a prodrug of a COX-2 selective inhibiting agent.

153. The method of claim 152 wherein the prodrug of a COX-2 inhibiting agent is parecoxib.

157. The method of claim 156 wherein the source of a COX-2 inhibiting agent is a source of a COX-2 selective inhibiting agent.

158. The method of claim 157 wherein the source of the COX-2 inhibiting agent is selected from the group consisting of celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, meloxicam, and ABT-963.

159. The method of claim 158 wherein the source of the COX-2 inhibiting agent is celecoxib.

160. The method of claim 158 wherein the source of the COX-2 inhibiting agent is valdecoxib.

161. The method of claim 158 wherein the source of the COX-2 inhibiting agent is deracoxib.

162. The method of claim 158 wherein the source of the COX-2 inhibiting agent is rofecoxib.

163. The method of claim 158 wherein the source of the COX-2 inhibiting agent is etoricoxib.

164. The method of claim 158 wherein the source of the COX-2 inhibiting agent is meloxicam.

165. The method of claim 158 wherein the source of the COX-2 inhibiting agent is ABT-963.

166. The method of claim 157 wherein the source of a COX-2 selective inhibiting agent is a chromene COX-2 selective inhibiting agent.

167. The method of claim 157 wherein the source of a COX-2 selective inhibiting agent is a prodrug of a COX-2 selective inhibiting agent.

168. The method of claim 167 wherein the produrg of a COX-2 selective inhibiting agent is parecoxib.

174. The method of claim 141 wherein the source of a COX-2 selective inhibiting agent is administered to the subject orally.

175. The method of claim 141 wherein the source of a COX-2 selective inhibiting agent is administered to the subject parenterally.

176. The method of claim 175 wherein the source of the COX-2 selective inhibiting agent is administered to the subject intravenously.

177. The method of claim 141 wherein the source of the COX-2 selective inhibiting agent is administered to the subject transdermally.

178. The method of claim 141 wherein the source of the COX-

2 selective inhibiting agent is administered to the subject rectally.

179. The method of claim 141 wherein the source of the **COX-2** selective inhibiting agent is administered to the subject before treating the subject with the DNA topoisomerase I inhibiting agent.

180. The method of claim 141 wherein the source of the **COX-2** selective inhibiting agent is administered to the subject concurrently with treating the subject with the DNA topoisomerase I inhibiting agent.

181. The method of claim 141 wherein the source of the **COX-2** selective inhibiting agent is administered to the subject after treating the subject with the DNA topoisomerase I inhibiting agent.

ACCESSION NUMBER: 2002:192070 USPATFULL
TITLE: Antiangiogenic **combination** therapy for the treatment of cancer
INVENTOR(S): **McKearn, John P.**, Wildwood, MO, UNITED STATES
Gordon, Gary B., Highland Park, IL, UNITED STATES
Cunningham, James, Chicago, IL, UNITED STATES
Gately, Stephen T., Palatine, IL, UNITED STATES
Koki, Alane T., Beaufort, MO, UNITED STATES
Masferrer, Jaime L., Ballwin, MO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002103141	A1	20020801
APPLICATION INFO.:	US 2001-843132	A1	20010425 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-470951, filed on 22 Dec 1999, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-113786P	19981223 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Pharmacia Corporation, Corporate Patent Department, P.O. Box 5110, Chicago, IL, 60680-9889
NUMBER OF CLAIMS: 181
EXEMPLARY CLAIM: 1
LINE COUNT: 8069
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L24 ANSWER 22 OF 60 USPATFULL

SUMM [0077] Conjunctive treatment of a compound of the present invention with another antineoplastic agent will produce a synergistic effect or alternatively reduce the toxic **side effects** associated with chemotherapy by reducing the therapeutic dose of the **side effect**-causing agent needed for therapeutic efficacy or by directly reducing symptoms of toxic **side effects** caused by the **side effect**-causing agent. A compound of the present invention will further be useful as an adjunct to **radiation** therapy to reduce **side effects** or enhance efficacy. In the present invention, another agent which can be combined therapeutically with a compound of the present invention includes any therapeutic agent which is capable of inhibiting the enzyme cyclooxygenase-2 ("**COX-2**"). Preferably such **COX-2** inhibiting agents inhibit **COX-2** selectively relative to the enzyme cyclooxygenase-1 ("COX-1"). Such a **COX-2** inhibitor is known as a "**COX-2** selective inhibitor". More preferably, a compound of the present invention can be therapeutically combined with a **COX-2** selective inhibitor wherein the **COX-2** selective inhibitor selectively inhibits **COX-2** at a ratio of at least 10:1 relative to inhibition of COX-1, more preferably at least 30:1, and still more preferably at least 50:1 in an in vitro test. **COX-2** selective inhibitors useful in therapeutic **combination** with the compounds of the present invention include celecoxib, valdecoxib, deracoxib, etoricoxib, rofecoxib, ABT-963 (2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1 -butoxy)-5-[4-(methylsulfonyl)phenyl-3(2H)-pyridazinone; described in PCT Patent Application No. WO 00/24719), or meloxicam. A compound of the present invention can also be advantageously used in therapeutic **combination** with a prodrug of a **COX-2** selective inhibitor, for example parecoxib.

PI US 2002019563 A1 20020214
US 6403830 B2 20020611

=> d 22 ibib

L24 ANSWER 22 OF 60 USPATFULL

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=> s ((adverse or side)(1w) effect) (1s) inflammat? (1s) fatigue (1s) (radi?)
L7            4 FILE EMBASE
L8            1 FILE CANCERLIT
L9            0 FILE TOXCENTER
L10           0 FILE MEDLINE
L11           1 FILE SCISEARCH
L12           0 FILE CAPLUS

TOTAL FOR ALL FILES

=> s fatigue (30a) (inflammatory response)
L14           8 FILE EMBASE
L15           3 FILE CANCERLIT
L16           2 FILE TOXCENTER
L17           6 FILE MEDLINE
L18           6 FILE SCISEARCH
L19           2 FILE CAPLUS

TOTAL FOR ALL FILES
L20          27 FATIGUE (30A) (INFLAMMATORY RESPONSE)

=> dup rem l20
PROCESSING COMPLETED FOR L20
L21          11 DUP REM L20 (16 DUPLICATES REMOVED)
                ANSWERS '1-8' FROM FILE EMBASE
                ANSWER '9' FROM FILE CANCERLIT
                ANSWERS '10-11' FROM FILE TOXCENTER

=> d 1-11 all


=> s fatigue (1s) (inflammatory response)
L23          42 FATIGUE (1S) (INFLAMMATORY RESPONSE)

=> s l23 not l22
L24          37 L23 NOT L22

=> d 10-37 hit, ibib
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L2 ANSWER 52 OF 52 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1986:48616 CAPLUS
DN 104:48616
TI Dynamic aspects of the in vitro chemotherapeutic activity of ansamycin (**rifabutine**) on Mycobacterium intracellulare
AU Perumal, Veluchamy K.; Gangadharam, Pattisapu R. J.; Heifets, Leonid B.; Iseman, Michael D.
CS Mycobacteriol. Res. Lab., Natl. Jew. Cent. Immunol. Respir. Med., Denver, CO, 80206-1997, USA
SO American Review of Respiratory Disease (1985), 132(6), 1278-80
CODEN: ARDSBL; ISSN: 0003-0805
DT Journal
LA English
CC 10-5 (Microbial Biochemistry)
Section cross-reference(s): 1
AB The in vitro action of ansamycin against M. intracellulare was studied using continuous, dynamic (rapidly falling off concn. simulating that existing in vivo in humans), and pulsed exposures. Ansamycin at a concn. of 5 .mu.g/mL showed bactericidal activity as early as 3 days after const. exposure. In the dynamic model with the drug present in bactericidal concn. for only 2 h a day, bactericidal activity was demonstrated. With pulsed exposure, a min. period of 72-96 h was necessary for effective inhibitory action.
ST ansamycin **chemotherapy** Mycobacterium; rifabutin **chemotherapy** Mycobacterium
IT Mycobacterium intracellulare
(ansamycin inhibition of)
IT 72559-06-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(chemotherapeutic activity of, on Mycobacterium intracellulare)

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:483986 CAPLUS
DN 135:136043
TI Induction of histidine decarboxylase in **inflammation** and immune responses
AU Endo, Yasuo
CS Dep. Pharmacol., Grad. Sch. Dent., Tohoku Univ., 4-1 Seiryo-machi, Aoba-ku, Sendai, 980-8575, Japan
SO Nippon Yakurigaku Zasshi (2001), 118(1), 5-14
CODEN: NYKZAU; ISSN: 0015-5691
PB Nippon Yakuri Gakkai
DT Journal; General Review
LA Japanese
CC 15-0 (Immunochemistry)
AB A review with 50 refs. Histamine is a classical, but still interesting **inflammatory** mediator. Many people have long believed that histamine is derived from mast cells or basophils alone. However, the histamine-forming enzyme, histidine decarboxylase (HDC), is induced in a variety of tissues in response (i) to gram-pos. and gram-neg. bacterial components (lipopolysaccharides, peptidoglycan, and enterotoxin A) and (ii) to various cytokines (IL-1, IL-3, IL-12, IL-18, TNF, G-CSF, and GM-CSF). HDC is induced even in mast-cell-deficient mice. The histamine newly formed via the induction of HDC is released immediately and may be involved in a variety of immune responses. Reviewing our work and that of Schayer and Kahlson, the pioneers in this field, lead us to the conclusion that nowadays we need to understand that histamine can be produced via the induction of HDC by a mechanism coupled with the cytokine network. We call this histamine "neohistamine", to distinguish it from the classical histamine derived from mast cells or basophils. Neohistamine is involved in physiol. reactions, **inflammation**, immune responses and a variety of diseases such as periodontitis, muscle **fatigue** (or temporamandibular disorders), stress- or **drug-induced** gastric ulcers, rheumatoid arthritis, complications in diabetes, hepatitis, allograft rejection, allergic reactions, tumor growth, and **inflammatory** side effects of aminobisphosphonates.
ST review histidine decarboxylase **inflammation** immune response; histamine cytokine histidine decarboxylase induction review
IT Immunity
Inflammation
(induction of histidine decarboxylase in **inflammation** and immune responses)
IT Cytokines
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(induction of histidine decarboxylase in **inflammation** and immune responses)
IT 51-45-6, Histamine, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(induction of histidine decarboxylase in **inflammation** and immune responses)
IT 9024-61-7, Histidine decarboxylase
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(induction of histidine decarboxylase in **inflammation** and immune responses)

L12 ANSWER 46 OF 50 USPATFULL on STN
ACCESSION NUMBER: 1998:98883 USPATFULL
TITLE: Peptide which abrogates TNF and/or LPS toxicity
INVENTOR(S): Rathjen, Deborah A., Sydney, Australia
Widmer, Fred, Sydney, Australia
Grigg, Geoffrey W., Sydney, Australia
Mack, Philip O., Sydney, Australia
PATENT ASSIGNEE(S): Peptide Technology Limited, Dee Why, Australia
(non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5795859		19980818	
	WO 9301211		19930121	
APPLICATION INFO.:	US 1994-178268		19940315	(8)
	WO 1992-AU332		19920703	
			19940315	PCT 371 date
			19940315	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	AU 1991-7097	19910705
	AU 1991-7924	19910822

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hutzell, Paula K.
ASSISTANT EXAMINER: Prickril, Benet
LEGAL REPRESENTATIVE: Nixon & Vanderhye P.C.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1243
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides peptides which have the ability to abrogate TNF toxicity and/or LPS toxicity. The present invention further relates to compositions including these peptides as the active ingredient and methods of anti-inflammatory treatment involving the administration of this composition. The peptides of the present invention are based primarily on residue 1 to 26 of human TNF.

SUMM The composition and method of the present invention would be expected to be useful as an anti-inflammatory agent in a wide range of disease states including toxic shock, adult respiratory distress syndrome, hypersensitivity pneumonitis, systemic lupus erythromatosis, cystic fibrosis, asthma, bronchitis, drug withdrawal, schistosomiasis, sepsis, rheumatoid arthritis, acquired immuno-deficiency syndrome, multiple sclerosis, leperosy, malaria, systemic vasculitis, bacterial meningitis, cachexia, dermatitis, psoriasis, diabetes, neuropathy associated with infection or autoimmnne disease, ischemia/reperfusion injury, encephalitis, Guillame Barre Syndrome, atherosclerosis, **chronic fatigue syndrome**, TB, other viral and parasitic diseases, OKT3 therapy, and would be expected to be useful in conjunction with **radiation** therapy, chemotherapy and transplantation, to ameliorate the toxic effects of such treatments or procedures,

=>

ion has been accomplished based on these findings.

SUMM As **causes** of ACMDS, there may be mentioned, for example, physical or psychological **fatigue**, stress, infections (for instance, **caused** by virus, bacteria, fungi, richettsia, protozoans, etc.), dysfunction or abnormality **caused** by cytokines (for example, interferon-.alpha., -.beta., -.gamma., interleukin-1 (IL-1), interleukin-2, (IL-2), tumor necrosis factor .alpha. (TNF.alpha.) and so on), malignant tumors, endocrine diseases, various types of metabolic disturbances, immunological abnormalities such as **autoimmune** diseases, chronic **fatigue** syndrome (CFS), chronic inflammatory diseases, thrombosis, embolism, neuro-muscular diseases, psychiatric diseases, drug abuse, toxicosis (poisoning) and others. When being complicated with ACMDS, the patient has further symptoms **caused** by ACMDS in addition to symptoms of the basal disease. Whereas a clear understanding of ACMDS has not been established for the present, such further symptoms related with or added by ACMDS are thought to be a series of symptoms accompanied with the basal disease.

L15 ANSWER 38 OF 59 USPATFULL on STN

SUMM As used herein, the term immune system refers to a system in an organism for defending itself from exogenous infection with virus, bacteria or the like, or from invasion of a human body with transformed cells (tumor cells and the like) formed by transformation of autologous cells. However, the immune system occasionally behaves abnormally, i.e., it functions excessively and acts to reject autologous components, or, on the other hand it sometimes functions deficiently, resulting in an immunocompromised state. Diseases resulting from these abnormal responses are generally called immunological diseases. Examples thereof include diverse diseases, for example, acute or chronic inflammatory diseases such as atopic cutaneous inflammatory diseases, pollinosis, asthma and sarcoidosis; **autoimmune** diseases such as allergic diseases, chronic rheumatoid arthritis, diabetes (IDDM), SLE and chronic **fatigue** syndrome; hepatitis, hepatic cirrhosis, inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn disease; and cancer cachexia. These immunological diseases originate from complex pathological **causes**. Systemic immunodeficiency and functional deficiency originate from pathological inflammation accompanied by cell proliferation, differentiation or cell necrosis through local production of cytokines or inflammatory mediators.

L15 ANSWER 26 OF 59 USPATFULL on STN

SUMM [0014] Polymyositis is a chronic connective tissue disease characterized by painful inflammation and degeneration of the muscles; dermatomyositis is polymyositis accompanied by skin inflammation. These diseases result in disabling muscle weakness and deterioration. The weakness typically occurs in the shoulders and hips but can affect muscles symmetrically throughout the body. Polymyositis and dermatomyositis usually occur in adults from ages 40 to 60 or in children from ages 5 to 15 years. Women are twice as likely as men to develop either disease. In adults, these diseases may occur alone or as part of other connective tissue diseases. The **cause** is unknown. Viruses or **autoimmune** reactions may play a role. Cancer may also trigger the diseases-an **autoimmune** reaction against cancer may be directed against a substance in the muscles as well. Symptoms, which may begin during or just after an infection, include muscle weakness (particularly in the upper arms, hips, and thighs), muscle and joint pain, Raynaud's phenomenon, a rash, difficulty in swallowing, a fever, **fatigue**, and weight loss. In dermatomyositis, rashes tend to appear at the same time as periods of muscle weakness and other symptoms.

L19 ANSWER 58 OF 96 USPATFULL on STN

SUMM Because the cellular mechanisms leading to cancer are so heterogeneous, research on such mechanisms is unlikely to yield a general approach to cancer treatment that is effective and well tolerated by cancer patients. Presently, a variety of non-specific treatment modalities are available, including surgery, **radiation**, and a variety of cytoreductive and hormone-based drugs, used alone or in combination. Some oncolytic drugs are also available, but the efficacy of these drugs varies among cancer types. Thus, patients suffering from cancer often are forced to undergo treatments that are highly non-specific and highly toxic. Commonly, the toxicity of the treatments produces severe **side** effects, including nausea and vomiting, hair loss, diarrhea, **fatigue**, ulcerations and the like, which severely impact the patient's quality of life. In some cases, the impact on the patient's quality of life can be so great that the patient is unable to continue the full course of therapy or opts out of treatment entirely.

PI US 5770613 19980623

L19 ANSWER 50 OF 96 USPATFULL on STN

DETD Turning now to FIGS. 7 and 8, an exemplary use of the **radiation** adjustment device is illustrated with respect to an external beam irradiation procedure for the male prostate. During conventional irradiation of the prostate, serious **side** effects may occur due to the resultant irradiation of areas of healthy tissue surrounding the prostate. These **side** effects may include diarrhea, intestinal discomfort, incontinence, **fatigue**, and impotence.

PI US 6066856 20000523

L19 ANSWER 44 OF 96 USPATFULL on STN

SUMM Either after or before surgery, **radiation** therapy may be recommended for rectal cancer. When given before surgery, the tumor can be shrunk, often making removal easier. **Radiation** therapy is rarely recommended for cancer of the colon. Treatment usually is done on an outpatient basis and involves five sessions per week for approximately six weeks. **Radiation** treatment can cause a number of **side** effects, including upset stomach, diarrhea, **fatigue** and skin irritation, which subside once treatment ends.

PI US 6251439 B1 20010626

L19 ANSWER 43 OF 96 USPATFULL on STN

SUMM **Radiation** therapy may be used to reduce the size of a tumor before surgery or to destroy cancer cells remaining in the breast, chest wall, or underarm area after surgery. The main **side** effects of **radiation** therapy are swelling and heaviness in the breast, sunburn-like skin changes in the treated area and possibly **fatigue**, but these changes to the breast tissue and skin usually go away in 6-12 months.

PI US 6277844 B1 20010821

L19 ANSWER 38 OF 96 USPATFULL on STN

SUMM [0019] Currently, methods of treatment for BPH and prostatic cancers include surgery, **radiation** therapy, and chemotherapy. The two most common operations for prostate cancer are radical prostatectomy and transurethral resection of the prostate (TURP). Radical prostatectomy removes the entire prostate gland and some tissue around it and carries a high risk of impotence and incontinence following surgery. The radical prostatectomy operation lasts from 1.5 to 4 hours, followed by an average hospital stay of three days and an average time away from work of three to five weeks. The TURP procedure last about 1 hours, followed by an average hospital stay of 1-2 days and 1-2 weeks time away from work and also has the **adverse side** effect of loss of bladder control. The **side** effects of **radiation** therapy can include diarrhea and irritated intestines, frequent urination, burning while urinating and blood in the urine, and a feeling of **tiredness**. **Side** effects of chemotherapy can include nausea and vomiting, loss of appetite, loss of hair, and mouth sores. Chemotherapy can also effect blood cells, which can increase the chance of infection, bleeding or bruising after minor injuries, as well as **tiredness**. Thus, alternative, non-invasive, treatments of BPH and prevention of prostate cancer are needed which have low toxicity and few **side** effects.

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